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CHROMOSOME 22q.11 DELETION
Recommendations for Diagnosis and Treatment

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AIMS

The recommendations on the management of patients with chromosome 22 deletion (del22) mark a turning point in the strategy adopted to date in formulating recommendations for the diagnosis and treatment of rare diseases. Previous documents referred to diseases in which an immunological defect was the predominant or even the only aspect of the disease. This facilitated the task of devising diagnostic and therapeutic guidelines focused on the immunological problem. By contrast, del22 syndrome is not one disease but a set of disorders sharing the same chromosome alteration. Initially described in DiGeorge syndrome, del22 was subsequently reported in other syndromes like velo-cardio-facial syndrome (VCSF), or “conotruncal anomaly face syndrome” (CTAFS). Appropriate care of patients with these conditions requires a team of specialists working together.

The basic aims of these recommendations are to:

- Collect a case series sharing the same underlying genetic defect;
- Define standard nationwide care recommendations;
- Monitor the natural history of the syndrome in relation to variations in clinical presentation;
- Devise increasingly effective treatment protocols to improve the quality of life of these patients by periodic updates on the clinical status and laboratory parameters of the patients enrolled.

The first part of these diagnostic and therapeutic recommendations addresses the pathophysiological mechanisms underlying the clinical and phenotypic spectrum of del22 syndrome.

The second part describes the diagnostic protocol, indicating patients’ inclusion criteria and the specialists involved in a full patient work-up.

The third part outlines the guidelines for the multidisciplinary management of these patients.

The fourth part deals with the problems of genetic risk, including screening for carrier status in women at risk, and prenatal diagnosis.

Lastly, the appendix mentions some more specialist immunological surveys which could be entertained in selected cases and hence after the protocol has been implemented.

Introduction

DELETION 22q.11 SYNDROME/ DiGEORGE SYNDROME

The association between thymic aplasia and congenital hypoparathyroidism was observed for the first time by Lobdell in 1959, but it was only in 1965 that these symptoms were ascribed to a new syndrome, DiGeorge syndrome (DGS), named after the doctor (Angelo DiGeorge) describing these symptoms in a group of children.

The incidence of this disease is 1/6000 and is caused by an embryogenetic defect of the structures deriving from the third and fourth branchial pouches between the fourth and sixth weeks of gestation. The thymus and inferior parathyroid glands derive from the third pouch while the superior parathyroid glands originate from the fourth pouch. The embryogenetic defect affects the development of the neural crest cells which play a decisive role in the development of the mesenchyme of these pouches that produces cartilage, muscles and blood vessels. The impaired development of epithelial elements derived from the third and fourth branchial pouches leads to: hypo/aplasia of the thymus, hypo/aplasia of the parathyroid glands, cardiac abnormalities and facial dysmorphisms.

These features give rise to the classic definition of DGS characterized by:

- Neonatal hypocalcaemic tetany;
- Immunodeficiency mainly affecting T cell immunity;
- Cardiac anomalies;
- facial dysmorphisms;

The DGS phenotype was initially confined to all or several of the above symptoms but almost all with the main diagnostic features of hypocalcaemia and/or immunodeficiency. With time the term has gradually been extended also to patients presenting only some of the classic symptoms, not necessarily associated with endocrine or immunological changes, like “velo-cardio-facial syndrome” (VCFS), or conotruncal anomaly face syndrome (CTAFS).

VCFS has been defined as the association of cleft palate, cardiac anomalies, language and learning difficulties and typical facies with velopharyngeal insufficiency resulting in a nasal voice.

CTAFS is characterized by cardiac defects like tetralogy of Fallot, transposition of the great vessels and double outlet right ventricle, etc. associated with facial anomalies (hypertelorism, epicanthus, narrow palpebral fissures, flat bridge nose, small mouth, freckles and malformed ears). The immunological and endocrinological defects are usually less severe both in VCFS and CTAFS.

The shared embryogenetic abnormalities of these three different syndromes have sometimes hampered the classification of a patient in one or another of these clinical forms. This difficulty was accounted for by the advent of in situ hybridization techniques which demonstrated that the three syndromes share a specific genetic alteration consisting in a deletion in hemizygosis of chromosome 22 at locus 22q11.2, present in around 90% of patients with DGS and in 70-90% of those with VCFS and CTAFS.

On the basis of these genetic and clinical observations and the inter and intrafamilial variability of the clinical phenotype, the term CATCH 22 was coined for a certain period of time to denote a syndrome including SDG, VCFS and CTAFS without distinction. The CATCH 22 acronym stands for the following:

C: Cardiac defects (mainly complex malformations of the cardiac outflow tract such as interrupted aortic arch and tetralogy of Fallot);

A: Abnormal facies;

T: Thymic hypo/aplasia (resulting in immunological abnormalities);

C: Cleft palate (open or beneath the submucosa or cleft uvula; short velum palatinum resulting in nasal voice is also typical);

H: Hypocalcaemia (due to impaired function of the parathyroid glands).

Nowadays the term CATCH 22 has passed into disuse due to its negative meaning, and the generic term “deletion 22” syndrome is preferred for all three syndromes. However newborns presenting cardiac defects associated with neonatal hypocalcaemia and/or immunodeficiency should be considered to have DGS, whereas school-age children with cleft palate and nasal voice with

language and learning difficulties probably have VCFS. Table I summarizes the clinical features of patients with chromosome 22 deletion syndrome.

Table I. Clinical features of patients with chromosome 22 deletion syndrome.

Cardiac anomalies	49%-83%
Tetralogy of Fallot	20%-45%
Interrupted aortic arch	5%-20%
Interventricular septal defect	5%-50%
Single arterial trunk	5%-10%
Hypocalcaemia	17%-60%
Palate defects	69%-100%
Cleft palate	9%-11%
Velopharyngeal insufficiency	27%-32%
Bifid uvula	5%
Kidney abnormalities	36%-37%
Agensis/dysplasia	17%
Obstruction	10%
Reflux	4%
Eye defects	7%-70%
Tortuous retinal vessels	58%
Anterior segment dysgenesis	69%
Neurological abnormalities	8%
Cerebral atrophy	1%
Cerebellar hypoplasia	0.4%
Dental defects (delayed tooth eruption, Enamel hypoplasia)	2.5%
Skeletal defects	17%-19%
Spinal anomalies	19%
Abnormal inferior extremities	15%
Language difficulties	79%-84%
Developmental delay	45%-75%
Behavioural abnormalities	9%-50%

Genetics of chromosome 22 deletion syndrome

DGS/VCFS is transmitted by an autosomal dominant mechanism. In 80% of cases deletion 22 arises de novo after conception by a pair of healthy parents, i.e. a couple without deletion 22. Instead, the deletion is family segregated in 20% of cases, i.e. inherited from one of the parents. A person with del22 has a 50% risk of recurrence for the disorder at each conception. Possible variable clinical expression of the syndrome has been described in affected subjects belonging to the same family.

The extension of del22q11.2 does not appear to be correlated to the severity of the phenotype. However, it cannot be ruled out that phenotypic variability depends on the extension of the deletion within the so-called “critical region” which includes different genes.

Around twenty genes have been identified in the chromosome region critical for DGS/VCFS on chromosome 22. Among the genes in this region the first to be investigated was HIRA (or TUPLE1) as it is implicated in the development of cardiac outflow tract septation with an expression pattern mimicking the pathogenetic mechanism of the neural crests. Animals were subsequently used to study the UFD1L and TBX1 genes, and TBX1 seems to play a particularly important role in the syndrome. An interesting recent finding was that some patients with the

DGS/VCFS phenotype without mental retardation do not have deletion 22 but present mutations in the TBX1 gene.

Clinical features

Facial anomalies

The faces of children with del 22 syndrome (SDG, VCFS, CFTAS) are usually long and thin. The most common dysmorphisms include: hypertelorism, narrow palpebral fissures with upward slant toward the exterior, periorbital fullness, prominent nose (with a bulbous tip and hypoplasia of the nares in younger children, “tubular” with a broad tip and hypoplasia of the nares in older children), short philtrum, small down-turned mouth tending to remain open with extroverse upper lip (“carp” mouth), high narrow palate, micrognathia, small ear pinnae with abnormal overfolded helices.

Cardiac anomalies

Congenital heart conditions are a common feature of the syndrome being present in around 75% of affected children and the commonest symptoms leading to diagnosis. They are also the most severe of the del22 defects and account for 50% of deaths. The clinical severity of the different heart diseases is inversely proportional to the age at onset of the various symptoms. The classic heart conditions encountered in these patients are truncoconal malformations consisting in abnormalities of the cardiac outflow tract. The commonest defects are: type B interrupted aortic arch, persistent arterial trunk, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, interventricular septal defects and isolated abnormalities of the aortic arch.

The less common cardiac defects include interatrial defect, double outflow right ventricle, aortic coarctation and transposition of the great arteries. Right arch vortex with aberrant subclavian artery is also common. Children with del 22q11 and truncoconal congenital cardiopathy have a prevalence of specific cardiac phenotypes consisting in associated cardiovascular abnormalities frequently characterizing the pattern of cardiac anatomy. The abnormalities associated with truncoconal malformations mainly affect the infundibular septum (hypoplastic or absent), the semilunar valves (stenotic or insufficient), the aortic arch (right, double or cervical) and the subclavian artery (aberrant).

Feeding disorders and gastrointestinal abnormalities

Feeding disorders and gastrointestinal abnormalities are important in del 22 syndrome. After cardiac defects feeding difficulties are the main disorder for which the parents of affected babies seek help. Typically infants have difficulty coordinating the suction/deglutition/breathing reflex resulting in slow feeding and episodes of regurgitation irrespective of anatomic heart and palate defects. The commonest disorders are: gastro-oesophageal reflux, oesophagitis and chronic constipation. The congenital abnormalities encountered in the syndrome include: oesophageal atresia, diaphragmatic herniation, congenital megacolon, anorectal malformations (atresia, anterior displacement) and dental anomalies such as delayed formation and eruption of permanent teeth and enamel hypoplasia.

Otolaryngological anomalies

Otolaryngological anomalies are found in 49% of patients with del22, the commonest being velopharyngeal insufficiency. Some patients have full-blown cleft palate whereas others present submucosal schisis. Harelip is less common. Hearing loss is frequently encountered in patients with del22 and consists of transmissive hypoacusia in 40% of cases. Most patients present abnormalities of the external auditory canal which may enhance the risk of infections like otitis media. Neurosensory deafness has been reported in 3% of cases. Laryngotracheal and oesophageal abnormalities, laryngomalacia, bronchomalacia, stenosis or atresia of the choanae and preauricular appendices or fistulae are also common.

Neurological and neuropsychological anomalies

Children with del22 may present: delayed acquisition of motor skills and language and learning difficulties with a wide variability in symptoms and age at onset among patients. Learning difficulties are found in 82-100% of cases. The intelligence quotient seems to vary between normal and moderate developmental delay with an average IQ of 70, whereas severe developmental deficits are seldom encountered in this syndrome. Many studies have reported a difference between verbal IQ and performance IQ in children and adolescents with deletion 22, i.e. a higher verbal IQ than performance IQ, as a sign of non-verbal cognitive disability, and they show a greater predisposition for reading and writing than arithmetic.

Psychiatric anomalies

Behavioural disorders in children include attention disorder with hyperactivity, emotional instability and anxiety, while adults sometimes present a tendency to psychotic episodes similar to schizophrenia.

Autoimmune anomalies

Autoimmune manifestations seen in 10% of cases may be part of the clinical spectrum of DGS. These patients may present idiopathic thrombocytopenic purpura and early onset polyarticular type juvenile rheumatoid arthritis. The prevalence of juvenile rheumatoid arthritis in children with DGS is significantly higher than that in the general population. Case of haemolytic anaemia and autoimmune pancytopenia, diabetes, autoimmune thyroid orbitopathy or Grave's disease, granulomatous hepatitis of probable autoimmune origin and vitiligo have also been described. The varied expression of the clinical phenotype associated with chromosome 22 deletion includes oligo/asymptomatic cases and could lead to an underestimation of autoimmune manifestations.

Endocrine anomalies

Neonatal hypocalcaemia secondary to hypoparathyroidism is common in these patients. Hypocalcaemia usually tends to normalize following compensatory parathyroid hypertrophy. A latent form of hypocalcaemic hypoparathyroidism has also been described in adolescence or later. These patients may develop transient or permanent hypocalcaemia in stressful situations such as surgical operations or severe infection. Abdominal pains may be a symptom of hypocalcaemia.

Immunological changes

Among patients with del22, the DiGeorge phenotype is the clinical form most commonly associated with immunological changes. Little is known about the immunological alterations present in VCFS or CFTAS as few immunological studies have addressed these two forms. For this reason most of the information in this section focuses on the DGS phenotype.

The main immunological defect encountered in patients with DGS is impaired T-cell function. Patients can be divided into two groups depending on the severity of the defect: patients with a partial immunological defect (pDGS) and patients with a complete immunological defect (cDGS). The complete form is rare (0.5-1.5%) and involves severe combined immunodeficiency (SCID) characterized by severe T cell depletion ranging from a major loss to absence of T lymphocytes due to impaired T cell production by the thymus and severely reduced lymphocyte proliferation whereas B cells are usually present. Differential diagnosis with other forms of T-B+ SCID may be difficult in the absence of early symptoms of hypocalcaemic tetany or heart defects and is aided by the finding of del22. By contrast, the immunological defect in pDGS is usually mild: the number of T cells is slightly reduced and the proliferative response to mitogens/antigens is usually normal or almost normal. These parameters often normalize over time and should be monitored at intervals depending on the age at which diagnosis was established. The response to mitogens is a better means of defining the severity of the immunological defect than the T cell count.

Although the distinction between cDGS and pDGS is currently deemed inaccurate as these forms represent only the endpoints of an "immunological continuum", the term cDGS continues to be used to indicate patients with a particularly severe immunological defect.

More recent immunological studies implementing advanced techniques to screen the T-cell repertoire (spectratyping) have disclosed major changes, largely confined to the CD8+ subpopulation. It is not yet known whether this result is due to the selection of certain clones following episodes of infection or whether it is the outcome of a primary thymic defect. Other studies have demonstrated a diminished percentage of CD4+CD25+ cells in DGS patients and this lymphocyte population seems to play a major role in building immunological tolerance and hence in preventing autoimmunity.

Variable changes in humoral immunity have also been reported in DGS, including an isolated IgA defect, hypogammaglobulinaemia, deficient antibody response to protein or polysaccharide antigens, and a defect in the IgG subclasses. It remains unsettled whether the humoral immune defect is secondary to T cell impairment or the outcome of a primary B cell defect.

The immunological changes reported account for the greater susceptibility to infections seen in patients with DGS. The immunological status of patients with 22 deletion but with a clinical phenotype more compatible with VCFS or CFTAS is poorly documented.

Other features

Children with Del 22q11.2 often have low birth weight and long slender fingers. Other features encountered more seldom include: kidney malformations (hydronephrosis, unilateral kidney agenesis, cystic kidney), genitourinary abnormalities (hypospadias, cryptorchidism, umbilical and inguinal herniations, uterine agenesis), malformations of the extremities (clubfoot, aplasia of the radius, syndactily, hypoplasia of the nails), orthopaedic abnormalities (kyphoscoliosis related to muscular hypotonia and spinal malformations) and ocular anomalies (corneal opacity, microphthalmia, coloboma of the iris).

2. DIAGNOSTIC PROTOCOL

Inclusion criteria

Male and female subjects of any age presenting del22 demonstrated by FISH will be enrolled. FISH analysis is recommended for all patients presenting **at least two of the following clinical features**:

1. Congenital cardiopathy

2. Palate abnormalities

At least one of the following:

- a. palatoschisis
- b. submucosal schisis of the palate
- c. velopharyngeal insufficiency
- d. bifid uvula

3. Neonatal hypocalcaemia

4. Immune and/or autoimmune defect

5. Facial dysmorphisms:

Concomitant presence of at least three of the following:

- a. narrow palpebral fissures
- b. prominent nose with bulbous tip (in newborns and infants)
prominent tubular nose (in children aged > 1 year)
- c. small “carp” mouth
- d. micrognathia
- e. dysmorphic ear pinnae

Any Centre not equipped for FISH analysis is invited to contact the Centre responsible for these recommendations.

A registration form (**Form 1.01**) and a diagnosis form (**Form 29.01**) will be filled in for FISH positive patients. Annual follow-up forms (**Form 29.02**) will then be filled in and sent to the AIEOP Operation Office in Bologna.

Tests at diagnosis:

At diagnosis:

Haemochrome

Electrolytes (total calcaemia, Calcium ions, Phosphorus)

Hormones (PTH, TSH, FT3, FT4)

Lymphocyte subpopulations (CD3,CD4,CD8,CD19,CD16, CD4CD45RA, CD4CD45RO, CD8CD45RA, CD8CD45RO)

Proliferation of T cells to mitogens (PHA)

IgG, IgA, IgM, IgE

Autoantibodies (ANA)

Cardiological assessment

All patients should undergo a cardiological assessment including: cardiological examination, ECG, and echocardiogram. Cardiac MR imaging should be entertained if vascular anomalies are suspected (echo positivity, dysphagia or dysphonia).

Neuropsychological assessment

Neuropsychological assessment involves a battery of tests. We list the most common tests used for a full neuropsychiatric investigation (Vicari and Caselli, 2002). The attending neurologist or neuropsychologist will decide which tests to administer from time to time depending on their availability at the various centres: Wechsler or Stanford-Binet intelligence scale; Peabody picture vocabulary test; language comprehension (Rustioni or Gettoni tests); object naming (Boston naming test); word production (FAS); aphasia (CAT); visual perception (VPT); visuomotor integration (VMI); word span; visuospatial span; long-term visuospatial learning; assessment of arithmetical skills.

Genetic assessment

The first genetic assessment includes: 1) a dysmorphological evaluation with a general examination; 2) screening tests for associated malformations; 3) an interview with parents to reconstruct the patient's family history.

The following dysmorphological features should be ascertained: facial dysmorphisms (narrow palpebral fissures, prominent nose with bulbous tip (in newborns and infants) or prominent tubular nose (in children aged > 1 year), small "carp" mouth, orbicular muscle hypoplasia, palate anomalies (cleft palate, submucosal schisis of the palate, bifid uvula), other anomalies like micrognathia, dysmorphic ear pinnae, preauricular fistulae/pedicles, hands with long slender fingers.

The following tests are used to screen for malformations: cerebral ultrasonography, eye examination, vertebral X-ray including the cervical spine, renal ultrasonography.

Otolaryngological/plastic surgery assessment

Audiometric examination and testing.

Gastroenterological assessment

Examination, growth parameters, digestive system abnormalities (e.g. oesophagitis, gastroesophageal reflux, oesophageal atresia, congenital megacolon), dental defects (delayed tooth formation and eruption, enamel hypoplasia, etc.).

During follow-up:

Every 12 months:

Haemochrome

Lymphocyte subpopulations

Proliferation of T cells to mitogens (PHA)

IgG, IgA, IgM, IgE

Autoantibodies (ANA)

IgG, IgA, IgM, IgE

Autoanticorpi (ANA)

FT3-FT4-TSH (if abnormal)

PTH (if abnormal)

Electrolytes (total calcaemia, calcium ions, phosphorus)

If diagnosis is established at birth the indications listed in the following scheme are recommended:

	Diagnosis	4 months of age	8 months of age	12 months of age
Lymphocyte subpopulations*	X	X	X	X
Proliferation of T cells to PHA	X ^a			X ^a
IgG, IgA, IgM, IgE	X		X	X
PTH	X			X ^a
TSH, FT3, FT4	X			X ^a

*= reassess every 12 months if abnormal

Cardiological assessment

Specialist cardiology and cardiosurgery centres suggest annual cardiological assessments for patients with heart defects whether or not they have undergone surgery.

Neuropsychological assessment

At diagnosis: administer the Stanford-Binet or Wechsler intelligence scale.

Schedule the following tests once or twice a year whenever possible:

Assessment of language comprehension, object naming, word production, aphasia and visual perception using the following tests:

Peabody picture vocabulary test;

Language comprehension (Gettoni test);

Object naming (Boston naming test);

Word production (FAS);

Aphasia (CAT);

Visual perception (VPT);

Visuomotor integration (VMI);

Word span;

Visuospatial span;

Long-term visuospatial learning;

Over six years of age: assessment of arithmetical skills.

Otolaryngological assessment

Annual ear examination and audiometric testing from the first to sixth years of life. After the age of seven ENT examinations should be scheduled if symptoms are present.

Annual plastic surgery examination to check the palate. Rhinoscopy after the age of seven (as indicated by the plastic surgeon).

3. TREATMENT RECOMMENDATIONS

The complexity of the myriad diseases sharing the same chromosome defect and the broad spectrum of clinical manifestations make it difficult to devise standard treatment recommendations for all patients.

The most appropriate treatment strategies must be implemented to tackle a single problem or range of problems.

The following recommendations concern the management of different clinical problems.

3.1 Recommendations on the management of immunological problems and infections

As already mentioned, any immunological defects encountered in patients with DGS or del22 vary in severity from an immunological status similar to T-B+ SCID to mild transient forms which tend to normalize over time. Between these two endpoints lie variable forms of immunological defect constituting a continuum.

Prophylaxis against *P. carinii*. This treatment is recommended in patients presenting a major CD4+ cell defect. The recommendations suggested for children with HIV infection can be applied: prophylaxis should be initiated if CD4+ cells are $< 750/\text{mm}^3$ in infants aged < 12 months; $< 500/\text{mm}^3$ in children aged between 1 and 5 years; $< 200/\text{mm}^3$ in children aged over 5 years. Treatment should be suspended as soon as the CD4+ cell count returns to normal.

Vaccinations. There are no contraindications to the administration of the vaccines scheduled for use in Italy in patients with DGS or del22 presenting a mild immunological defect. Live attenuated vaccines can be administered if the proliferative response to mitogens is normal, the maximum number of CD4+ lymphocytes is $> 500/\text{mm}^3$ and the absolute number of CD8+ lymphocytes is $> 400/\text{mm}^3$. If these parameters are not met it is preferable to postpone vaccination. These patients must be followed over time also because immunological parameters may normalize even after the first year of life.

Administration of vaccines constituted by purified antigens (tetanus, diphtheria, whooping cough, hepatitis, *H. influenzae*, anti-influenza, antipneumococcus) are recommended in all patients. Immunisation carries no risk but the antibody response will depend on the severity of the immunological defect.

Antibiotic prophylaxis. Children with DGS or del22 may have an enhanced susceptibility to infections which is partly due to the immune defect and partly the facial anomalies predisposing to enhanced susceptibility to upper airway infections. Prompt aggressive antibiotic treatment is recommended in all cases to control acute episodes of infection. Antibiotic prophylaxis can also be entertained in case of recurrent infection and its duration must be determined in individual cases by the attending physician.

Intravenous immunoglobulin replacement therapy. The immune defect in del22 is usually mild and does not require intravenous immunoglobulin replacement therapy unless patients are clinically symptomatic.

IVIg therapy may be indicated in forms of del22 presenting severe T cell depletion similar to that observed in SCID.

Transplantation of thymic tissue or bone marrow. Rare patients with del22 presenting a particularly severe phenotype similar to that encountered in SCID patients have received transplants of thymic tissue taken from donors younger than six months undergoing heart surgery, when much of the thymus needs to be resected to allow surgical access. In this approach the haematopoietic cell component must be completely removed to avoid GVHD and allow the epithelial component of the

thymus to enter into contact with the stem cells of the transplant recipient. Results appear encouraging but long-term validation is required.

Bone marrow transplantation was performed in the past but is currently not indicated as the defect is intrinsic to the thymus. Likewise, infusion of the haematopoietic component obtained from foetal thymus (incorrectly termed “transplantation of foetal thymus”) is obsolete due to the high risk of GVHD caused by the lack of HLA identical donors, and should not be undertaken in the light of current knowledge.

3.2 Recommendations on the management of cardiological problems

Once a cardiopathy has been established, the patient must be referred to a tertiary care centre specialised in paediatric cardiology and cardiosurgery as cardiac catheterism and urgent cardiosurgery intervention may be indicated in some cases. Other cases will require clinical follow-up with periodic examinations and instrumental tests to be prescribed by specialists.

Cardiosurgery candidates must undergo a thorough pre-operative work-up of apparatuses other than the heart as immunological, tracheoparyngeal, oesophageal, gastrointestinal or renal abnormalities may affect the immediate post-operative period and surgical outcome.

If transfusions are required irradiated products should be used to avoid GVHD. Peri-operative antimicrobial prophylaxis with glycopeptides and aminoglycosides is also recommended along with peri-operative antifungal prophylaxis in patients with CD4 depletion.

3.3 Recommendations on the management of neuropsychiatric problems.

The clinical approach to caring for del22 patients presenting neuropsychological and/or psychiatric problems must address the patient’s specific problem(s) in order to devise a global multidisciplinary care schedule involving different specialists to be coordinated by the attending neuropsychiatrist.

3.4 Recommendations on the management of other problems (feeding/gastrointestinal, ENT, etc.)

Different specialists must be involved in the management of specific gastrointestinal and/or otolaryngological problems, etc. to devise exercises facilitating chewing and swallowing.

ENT specialists will be involved in the management of velopharyngeal insufficiency, hearing loss, cleft lip/palate or laryngotracheal abnormalities. Please note that adenoidectomy is contraindicated in patients with velopharyngeal insufficiency as adenoid resection exacerbates this insufficiency.

4. PREVENTION

Genetic counselling

Most chromosome 22 deletions occur sporadically. However, the deletion can be transmitted as a dominant trait. A patient with DGS has a 50% probability of transmitting the chromosome bearing the deletion to his/her offspring. The size of the deletion is not correlated to the severity of the clinical phenotype making it difficult to predict the expected phenotype on the basis of the deletion alone. In addition, phenotypic variations exist within the same family ranging from a classic form of DGS to forms with mild facial dysmorphisms, learning difficulties and nasal voice, so that parents will remain without a diagnosis until a child is born with a phenotype evidencing disease.

Prenatal diagnostic testing for del22 can be done on amniocytes or chorionic villi obtained from pregnant women at risk for FISH positivity. In addition to pregnancies at risk for del22, there are also pregnancies in which echocardiography or ultrasound disclose compatible heart defects or cleft palate. However mild malformations like submucosal cleft palate and mild dysmorphic traits may go undetected.

It is difficult to counsel DGS patients without the chromosome deletion because a small del22 may not be identified by the probe used. In addition a few DGS patients may have deletions of the short arm of chromosome 10.

Foetal ultrasound investigation and echocardiography are currently the only tools available to identify pregnancies without del22 or other chromosome defects which may be at risk.

Disease carrier status

Identification of disease carrier status is essential for genetic counselling and FISH analysis is recommended for the parents of each patient enrolled. The results of the test must be inserted on the diagnosis form (**Form 29.01**).

5. APPENDIX

The del22 register could offer a unique possibility to undertake in-depth immunological studies designed to better define the pathogenetic aspects of the syndrome after a sufficient number of patients have been enrolled. The results yielded by the implementation of the protocol should allow us to devise proposals for more advanced immunological analysis for the purposes of research rather than care.

Future investigations include:

- assessment of the different B cell subpopulations;
- analysis of T regulatory cells;
- analysis of the T lymphocyte repertoire by spectratyping and TRECS assessment;
- assessment of antibody response to polysaccharide antigens.

The following blood samples are required for these analyses:

- 3 cc whole blood in EDTA for B cell analysis
- 2 cc whole blood in EDTA for analysis of regulatory T cells
- 3 cc for the study of the T cell repertoire and TRECS
- 1 cc serum for the assessment of antibody response to polysaccharide antigens.

The local Centre will send blood samples with prior notice to the Centres listed below depending on the analysis required. Samples must be sent by a courier guaranteeing delivery within 24h:

Assessment of the different B cell subpopulations;
Analysis of T regulatory cells
Dr. Rita Carsetti/Dr. Silvia Di Cesare
Laboratorio Immunologia e Biotecnologia pediatrica
Ospedale Bambino Gesù/Università Tor Vergata
Torre E Nord 5° piano
Via di Tor Vergata,135
0133 Roma
Tel.067256823/6825

Molecular study of the T cell repertoire (spectratyping) and TRECS:
Dr. MariaLuisa Romiti/ Dr. Caterina Cancrini
Laboratorio Immunologia e Biotecnologia pediatrica
Ospedale Bambino Gesù/Università Tor Vergata
Torre E Nord 5° piano
Tel.067256492/6824
Via di Tor Vergata,135
0133 Roma

Antipneumococcal polysaccharide antibody response (1ml serum)
Prof. Isabella Quinti
Dipart. Medicina Clinica
Università La Sapienza
Viale dell'Università,37
00186 ROMA
tel. 06/49972 036
fax/4466209

6. REFERENCES

- ELIEZ S, BLASEY CM, MENON V, WHITE CD, SCHMITT JE, REISS AL. Functional brain imaging study of mathematical reasoning abilities in velocardiofacial syndrome (del22q11.2), *Genet Med*, 2001 Jan-Feb; 3(1):49-55;
- DIGILIO MC, ANGIONI A, DE SANTIS M, LOMBARDO ET AL. Spectrum of clinical variability in familial deletion 22q11.2: from full manifestation to extremely mild clinical anomalies, *Clin Genet*, 2003 Apr;63(4):308-13;
- Driscoll DA, Spinner NB, Budarf ML, McDonald-McGinn DM, Zackai EH, Goldberg RB, Shprintzen RJ, Saal HM, Zonana J, Jones MC, et al. Deletions and microdeletions of 22q11.2 in velo-cardio-facial syndrome. *Am J Med Genet* 1992 Sep 15;44(2):261-8
- DRISCOLL DA, SALVIN J, SELLINGER B, ET AL. Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis, *J Med Genet*, 1993; 30: 813-817;
- MCDONALD-MCGINN DM, KIRSCHNER R, GOLDMUNTZ E, SULLIVAN K ET AL. The Philadelphia story: the 22q11.2 deletion: report on 250 patients, *Genet Couns*, 1999;10(1):11-24.
- PEREZ E, SULLIVAN KE. Chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes), *Curr Opin Pediatr*, 2002 Dec;14(6):678-83;
- 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 Jan-Feb;3(1):34-9;
- JEROME LA & PAPAIOANNOU VE. DiGeorge syndrome phenotype in mice mutant for the T-box gene, *Tbx1*, *Nature Genet*, 2001; 27: 286-291;
- DEVRIENDT K, FRYNS J-P, MORTIER G. The annual incidence of DiGeorge/ velocardiofacial syndrome, *J Med Genet*, 1998; 35: 789-790;
- BOTTO LD, MAY K, FERNHOFF PM, CORREA A, COLEMAN K, RASMUSSEN SA, MERRITT RK, O'LEARY LA, WONG LY, ELIXSON EM, MAHLE WT, CAMPBELL RM. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics* 2003;112:101-107
- Cuneo BF. 22q11.2 deletion syndrome: DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes. *Curr Opin Pediatr*. 2001 Oct;13(5):465-72.
- HUANG RY, SHAPIRO NL. Structural airway anomalies in patients with DiGeorge syndrome: a current review. *Am J Otolaryngol*. 2000 Sep-Oct;21(5):326-30.
- RYAN AK, GOODSHIP JA, WILSON DI, PHILIP N, LEVY A, SEIDEL H, SCHUFFENAUER S, OECHSLER H, BELOHRADSKY B, PRIEUR M, AURIAS A, RAYMONDFL, CILAYTON-SMITH J, HATCHWELLE, MCKEON C, BEEMER FA, DALLAPICCOLA B, NOVELLI G, HURST JA, IGANTIUS J, GREEN AJ, WINTER RM, BRUETON L, BRONDUM-NIELSEN K, SCAMBLER PJ, et al. Spectrum of clinical features associated with interstitial chromosome 22q11.2 deletion: a European collaborative study *J Med Genet*. 1997 Oct;34(10):798-80;
- ANDERSSON GÄRE B, FASTH A, Epidemiology of juvenile chronic arthritis in southwestern Sweden: A 5-year prospective population study, *Pediatrics*, 1992; 90:950-958;
- ASANO M, M TODA, N SAKAGUCHI, ET AL. Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation, *J Exp Med*, 1996; 184:387-396;
- AUGUST CS, ROSEN FS, FILLER RM, ET AL. Implantation of a foetal thymus, restoring immunological competence in a patient with thymic aplasia (DiGeorge's syndrome), *Lancet*, 1968; 2:1210-1211;
- BALE PM, SOTELO-AVILA C. Malescent of the thymus: 34 necropsy and 10 surgical cases, including 7 thymuses medial to the mandible, *Pediatr Pathol*, 1993 Mar-Apr; 13:181-90;
- BARRETT DJ, AMMANN AJ, WARA DW ET AL. Clinical and immunologic spectrum of the DiGeorge syndrome. *J Clin Lab Immunol*. 1981 Jul; 6:1-6;
- BASTIAN J, LAW S, VOGLER L, LAWTON A ET AL. Prediction of persistent immunodeficiency in the DiGeorge anomaly, *J Pediatr*, 1989 Sep;115:391-396;
- CHINEN J, ROSENBLATT HM, SMITH EO, ET AL. Long-term assessment of T-cell populations in DiGeorge syndrome, *J Allergy Clin Immunol*, 2003 Mar;111(3):573-579;
- COLLARD HR, BOECK A, MCLAUGHLIN TM, ET AL, Possible extrathymic development of non-functional T cells in a patient with complete DiGeorge syndrome, *Clin Immunol*, 1999; 91:156-162;

- CONLEY ME, BECKWITH JB, MANCER JF, TENCKHOFF L. The spectrum of the DiGeorge syndrome, *J Pediatr*, 1979 Jun; 94(6):883-890;
- DE PIERO A, LOURIE EM, BERMAN BW, ET AL. Recurrent immune cytopenias in two patients with DiGeorge/velocardiofacial syndrome, *J Pediatr*, 1997; 131:484-486;
- DIGEORGE A. A new concept of the cellular basis of immunity, *J Pediatr*, 1965; (67)907;
- ELDER DA, KAISER-ROGERS K, AYLOS WORTH AS, ET AL. Type I diabetes mellitus in a patient with chromosome 22q11.2 deletion syndrome, *Am J Med Genet*, 2001; 101: 17-19;
- ETZIONI A, POLLACK S. Hypogammaglobulinemia in DiGeorge sequence, *Eur J Pediatr*, 1989;150:144-5;
- FLATO B, AASLAND A, VINJE O, ET AL. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthritis, *J Rheumatol*, 1998; 25:366-75;
- GENNERY AR, BARGE D, O'SULLIVAN JJ ET AL. Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome, *Arch Dis Child*, 2002 Jun;86(6):422-5;
- GODTHELP BC, VAN EGGERMOND MCJA, PEIJNENBURG AD ET AL. Incomplete T cell immunoreconstitution in two major histocompatibility complex class II-deficiency/Bare lymphocyte syndrome patients after HLA-identical sibling bone marrow transplantation, *Blood*, 1999; 94: 348-58;
- GOLDSOBEL AB, HAAS A, STIEHM ER. Bone marrow transplantation in DiGeorge syndrome, *J Pediatr*, 1987; 111:40-44;
- GORSKI J, YASSAI M, ZHU X ET AL. Circulating T cell repertoire complexity in normal individuals and bone marrow recipients analyzed by CDR3 size spectratyping, *J Immunol*, 1994; 152: 5109-19;
- GUPTA S, AGGARWAL S, NGUYEN T. Increased spontaneous apoptosis in T lymphocytes in DiGeorge anomaly, *Clin Exp Immunol*, 1998 Jul;113(1):65-71;
- JAVIER CHINEN , MD, PHD, HOWARD M.ROSENBLATT, ET AL. Long-term assessment of T-cell populations in DiGeorge syndrome, *J Allergy Clin Immunol*, 2003; Vol 111: n° 3;
- JAWAD FA, MCDONALD-MCGINN DM, ZACKAI E, ET AL. Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge Syndrome/ Velocardiofacial syndrome), *J Pediatr*, 2001;139:715-23;
- JUNKER AK, DRISCOLL DA. Humoral immunity in DiGeorge syndrome, *J Pediatr*, 1995 Aug;127(2):231-7;
- KATHLEEN E. SULLIVAN, DONNA MCDONALD-MCGINN, ELAINE H. ZACKAI. CD4+ CD25+ T-Cell production in healthy humans and in patients with thymic hypoplasia, *Clinical and Diagnostic Laboratory Immunology*, 2002; 1129-1131;
- KORNFELD SJ, ZEFFREN B, CHRISTODOULOU CS, ET AL. DiGeorge anomaly: a comparative study of the clinical and immunologic characteristics of patients positive and negative by fluorescence in situ hybridization, *J Allergy Clin Immunol*, 2000;105:983-987;
- MARKERT ML, BOECK A, HALE LP, KLOSTER AL ET AL. Transplantation of thymus tissue in complete DiGeorge syndrome, *N Engl J Med*, 1999 Oct 14;341(16):1180-9;
- MARKERT ML, HUMMELL DS, ROSENBLATT HM, ET AL. Complete DiGeorge syndrome: persistence of profound immunodeficiency, *J Pediatr*, 1998; 132:15-21;
- MAYUMI M, KIMATA H, SUEHIRO Y, ET AL. DiGeorge syndrome with hypogammaglobulinemia: a patient with excess suppressor T cell activity treated with fetal thymus transplantation, *Eur J Pediatr*, 1989; 148:512-22;
- MCDONALD-MCGINN DM, KIRSCHNER R, GOLDMUNTZ E, SULLIVAN K ET AL. The Philadelphia story: the 22q11.2 deletion: report on 250 patients, *Genet Couns*, 1999;10(1):11-24.
- MULLER W, PETER HH, KALLFELZ HC, ET AL. The DiGeorge sequence. II. Immunological findings in partial and complete forms of the disorder, *Eur J Pediatr*, 1989; 19:96-103;
- PINCHAS-HAMIEL O, MANDEL M, ENGELBERG S, ET AL. Immune hemolytic anaemia, thrombocytopenia and liver disease in a patient with DiGeorge syndrome, *Isr J Med Sci*, 1994; 30:530-532;
- RASMUSSEN SA, WILLIAMS CA, AYOUB EM, ET AL. Juvenile rheumatoid arthritis in velo-cardio-facial syndrome : coincidence or unusual complication?, *Am J Med Genet*, 1996; 64:546-550;
- SCHUBERT MS, MOSS RB. Selective polysaccharide antibody deficiency in familial DiGeorge syndrome, *Ann Allergy*, 1992; 69:231-8;
- SIRIANNI MC, BUSINCO L, FIORE L, SEMINARA R, AIUTI F. T-cell subsets and natural killer cells in DiGeorge and SCID patients, *Birth Defects Orig Artic Ser*, 1983;19(3):107-8;
- SMITH CA, DRISCOLL DA, EMANUEL BS, ET AL. Increased prevalence of immunoglobulin A deficiency in patients with the chromosome 22q11.2 deletion syndrome, *Clin Immunol Immunopathol*, 1998; 86:141-6

- SULLIVAN KE, MCDONALD-MCGINN D, DRISCOLL DA, ET AL. Longitudinal analysis of lymphocyte function and numbers in the first year of life in chromosome 22q11.2 deletion syndrome (DiGeorge Syndrome/Velocardiofacial syndrome), *Clin Diagn Lab Immunol*, 1999; 6:906-11;
- F.AMATI, A.MARI, M.C.DIGILIO, R.MINGARELLI, B.MARINO, A.GIANNOTTI, G.NOVELLI, B.DALLAPICCOLA. *22q11 deletions in isolated and syndromic patients with tetralogy of Fallot*. *Hum Genet* 1995; 95: 479-82
- B.MARINO, M.C. DIGILIO, A. TOSCANO, S. ANACLERIO, A. GIANNOTTI, C. FELTRI, M.A. DE IORIS, A. ANGIONI, B. DALLAPICCOLA. *Anatomic patterns of conotruncal defects associated with deletion 22q11*. *Genetics in Medicine* 2001;3(1):45-48
- M.C. DIGILIO, B. MARINO, M. CAPPA, P. CAMBIASO, A. GIANNOTTI, B. DALLAPICCOLA. *Auxological evaluation in patients with DiGeorge/velocardiofacial syndrome (deletion 22q11 syndrome)*. *Genetics in Medicine* 2001;3(1):30-33.
- A. TOSCANO, S. ANACLERIO, M.C. DIGILIO, A. GIANNOTTI, G. FARIELLO, B. DALLAPICCOLA, B. MARINO. *Ventricular septal defect and deletion of chromosome 22q11: anatomical types and aortic arch anomalies*. *Eur J Pediatr* 2002; 161: 116-117.
- M. PIERDOMINICI, F. MAZZETTA, E. CAPRINI, M. MARZIALI, M.C. DIGILIO, B. MARINO, A. AIUTI, F.AMATI, G. RUSSO, G. NOVELLI, F. PANDOLFI, G. LUZI, A. GIOVANNETTI. *Biased T-cell receptor repertoires in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome)*. *Clin Exp Immunol* 2003;132:323-31.
- S. ANACLERIO, V. DI CIOMMO, G. MICHIELON, M.C. DIGILIO, R. FORMIGARI, F.M. PICCHIO, G. GARGIULO, R. DI DONATO, M.A. DE IORIS, B. MARINO. *Conotruncal heart defects: impact of genetic syndromes on immediate operative mortality*. *Ital Heart J* 2004;5:624-628.
- VICARI S. e CASELLI M.C. (a cura). *I Disturbi dello Sviluppo. Neuropsicologia clinica e ipotesi riabilitative*. Il Mulino Ed., Bologna, 2002.
- PIGNATA C., D'AGOSTINO A., FINELLI P., FIORE M., SCOTESI I., COSENTINI E., CUOMO C., VENUTA S. *Progressive deficiencies in blood T cells associated with a 10p12-13 interstitial deletion*. *Clin. Immunol. Immunopathol.* 1996; 90: 9-15.
- GREENBERG F, ELDER FFB., HAFFNER P., NORTHRUP H., LEDBETTER DH. *Cytogenetic findings in a prospective series of patient with Di George anomaly*. *Am J Hum Genet* 1988; 43:605-11.