22q11DS European Conference

Barcelona, November 16-17 2019

Auditorium at Disseny Hub

Management of physical issues in 22q11DS

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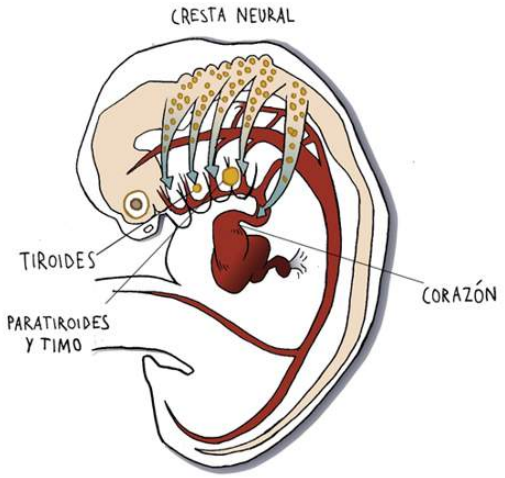
Enfermedades Raras

General considerations

- Multisystemic condition
- Consistent pattern, variable
- Presence and severity of features varies by age
- Significant morbidity in lifetime
- Requires multidisciplinary management
- Early diagnosis and effective treatment of associated problems improves general outcome

- Congenital heart disease (75%)
- VPI (65%), cleft palate (11%)
- Immunodeficiency (75%)
- Hypocalcemia (50%)
- Hypothyroidism (20%)
- Feeding difficulties
- Gastrointestinal (30%)
- Genitourinary (30%)
- Distinctive facial features
- Developmental delay
- Learning difficulties
- Behaviour problems
- Increased risk for psychosis



(Adapted from Scambler. Hum Mol Genet 2000)

- Congenital heart defect
- Feeding difficulties, poor weight gain
- Slow development, hypotonic, delayed speech
- Recurrent respiratory and middle ear infectious ("sickly child")
- Growth at lower end normal range
- Nasal speech (VPI)
- Poor social skills, timid, introverted
- Learning difficulties
- Refractive error, glasses
- Too many visits to hospital and health professionals

- It may present at differents ages with different medical problems

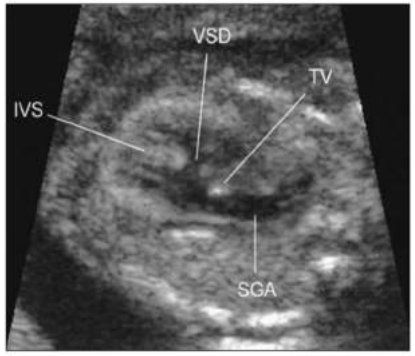


Figure 1. Sonogram of the fetal heart showing an abnormal cardiac axis, a VSD, and a single great artery (SGA) with an echogenic thickened valve (TV) straddling the interventricular septum (IVS).

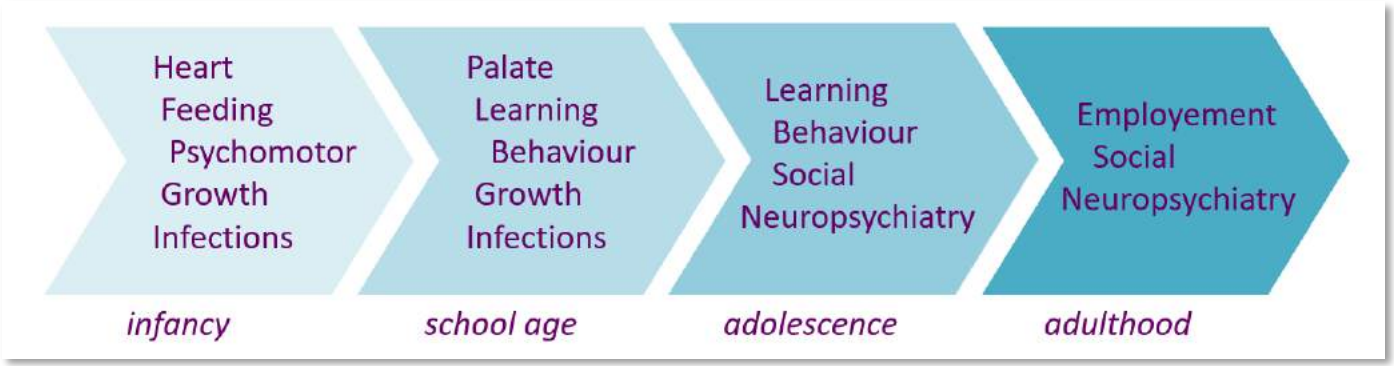
• Truncus arteriosus

• Autoimmune pancytopenia
• No CHD
• Laryngeal web, no VPI

• Submucosal cleft palate, VPI
• No CHD
• Learning difficulties

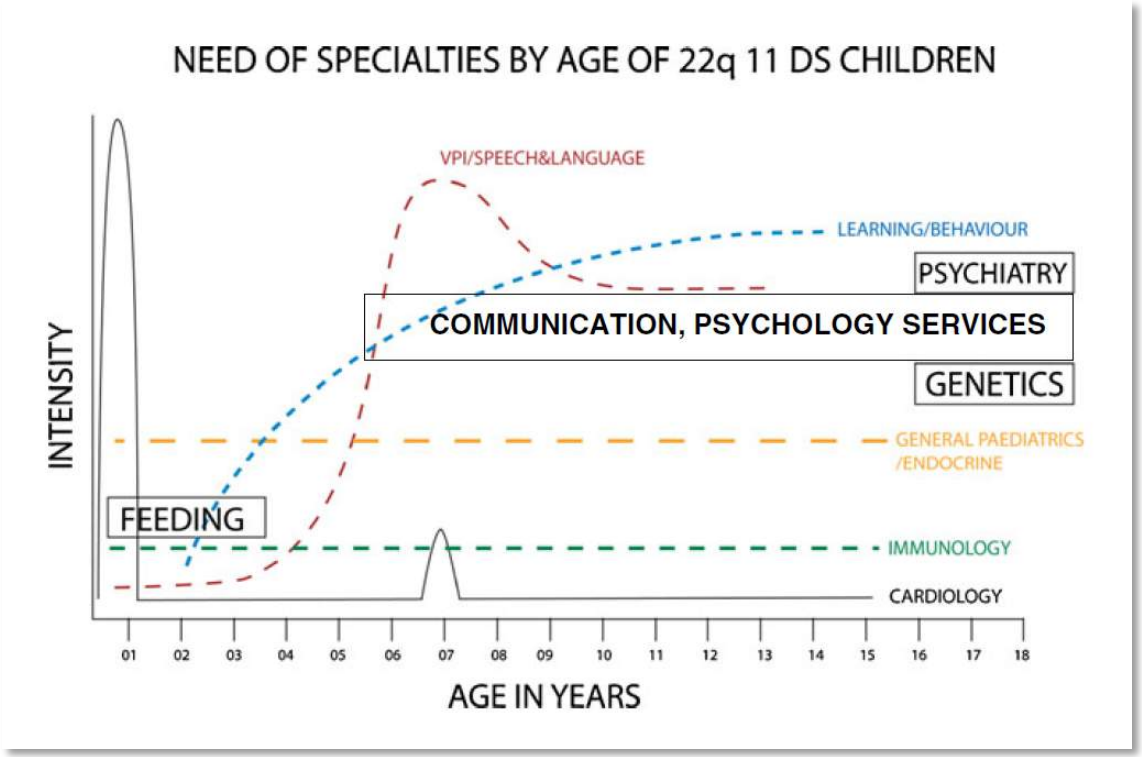
• Intellectual disability
• Psychotic symptoms
• No CHD

- Medical, educational, social and neuropsychiatric concerns have different priorities at different stages of life



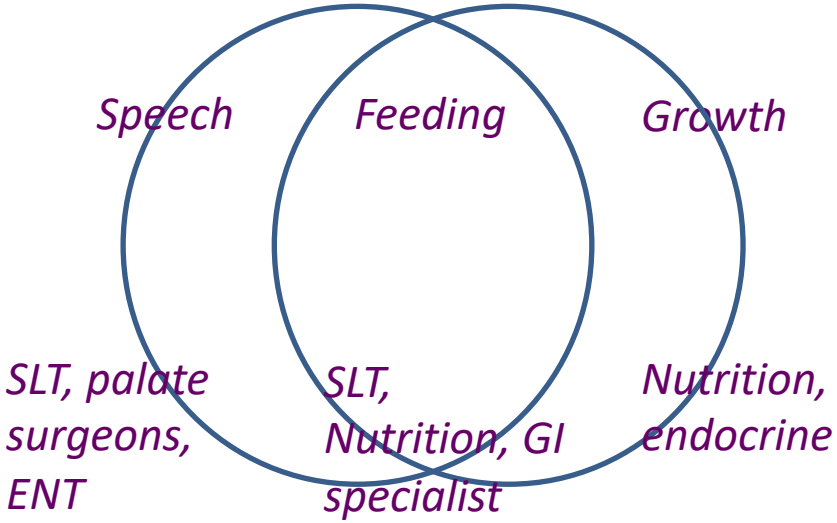
(Adapted from Kobrinsky and Sullivan. Lancet 2007)

- Medical, educational, social and neuropsychiatric concerns have different priorities at different stages of life



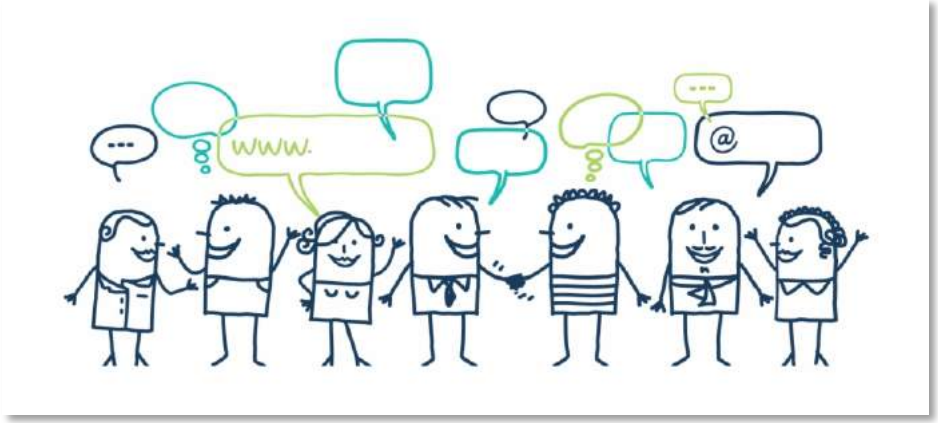
(Habel et al. Eur J Pediatr 2014)

- Simultaneous and overlapping aspects of development



General considerations

- Multisystemic disorder, multidisciplinary approach
- Management coordinator: Facilitate communication between specialists, ensure adherence to guidelines

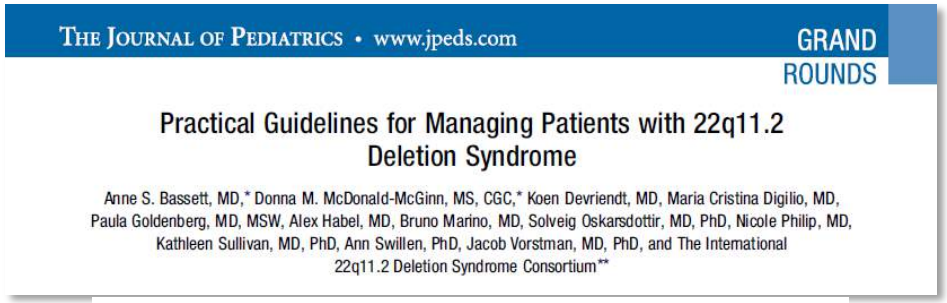


- Involve family members, school teachers and non-health specialists (social work, occupational therapy)

- Ensure smooth transition to adult specialists, avoid gaps in care

22q11DS: Management and implementation of clinical guidelines
Available guidelines

- Guidelines developed based on consensus of experts
- Individual management plan



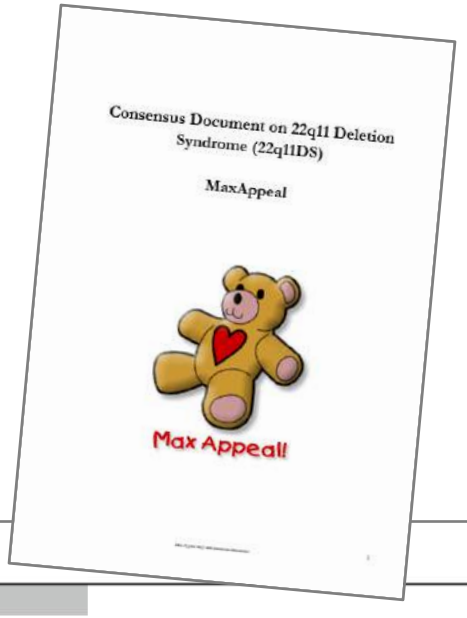
THE JOURNAL OF PEDIATRICS • www.jpeds.com GRAND ROUNDS

Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome

Anne S. Bassett, MD,* Donna M. McDonald-McGinn, MS, CGC,* Koen Devriendt, MD, Maria Cristina Digilio, MD, Paula Goldenberg, MD, MSW, Alex Habel, MD, Bruno Marino, MD, Solveig Oskarsdottir, MD, PhD, Nicole Philip, MD, Kathleen Sullivan, MD, PhD, Ann Swillen, PhD, Jacob Vorstman, MD, PhD, and The International 22q11.2 Deletion Syndrome Consortium**

Table II. Recommended assessments for 22q11.2 deletion syndrome*

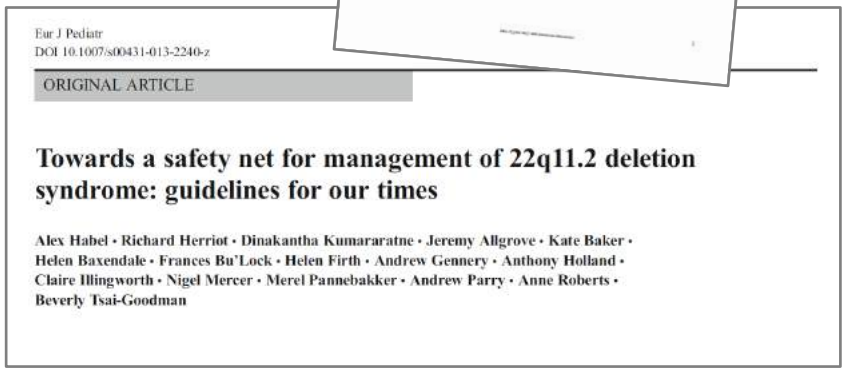
Assessment	At diagnosis	Infancy (0-12 months)	Preschool age (1-5 years)	School age (6-11 years)	Adolescence (12-18 years)	Adulthood (>18 years)
Ionized calcium, parathyroid hormone†	✓	✓	✓	✓	✓	✓
Thyrotropin (thyroid-stimulating hormone)†	✓		✓	✓	✓	✓
Complete blood cell count and differential (annual)	✓	✓	✓	✓	✓	✓
Immunologic evaluation‡	✓	✓§	✓§			
Ophthalmology	✓		✓			
Evaluate palate¶	✓	✓	✓			
Audiology	✓	✓	✓			✓
Cervical spine (>age 4 years)			✓‖			
Scoliosis examination	✓		✓		✓	
Dental evaluation			✓	✓	✓	✓
Renal ultrasound	✓					
Electrocardiogram	✓					✓
Echocardiogram	✓					
Development**	✓	✓	✓			
School performance				✓	✓	
Socialization/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioral††	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counseling‡‡	✓				✓	✓
Gynecologic and contraceptive services					✓	✓



Consensus Document on 22q11 Deletion Syndrome (22q11DS)

MaxAppeal

Max Appeal!



Eur J Pediatr
DOI 10.1007/s00431-013-2240-z

ORIGINAL ARTICLE

Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times

Alex Habel · Richard Herriot · Dinakantha Kumararatne · Jeremy Allgrove · Kate Baker · Helen Baxendale · Frances Bu'Lock · Helen Firth · Andrew Gennery · Anthony Holland · Claire Illingworth · Nigel Mercer · Merel Pannebakker · Andrew Parry · Anne Roberts · Beverly Tsai-Goodman

- Guidelines developed based on consensus of experts

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Complete blood cell count and differential (annual)	✓	✓	✓	✓	✓	✓
Immunologic evaluation‡	✓	✓§	✓§			
Ophthalmology	✓		✓			
Evaluate palate¶	✓	✓	✓			
Audiology	✓	✓	✓			✓
Cervical spine (>age 4 years)			✓‖			
Scoliosis examination	✓		✓		✓	
Dental evaluation			✓	✓	✓	✓
Renal ultrasound	✓					
Electrocardiogram	✓					✓
Echocardiogram	✓					
Development**	✓	✓	✓			
School performance				✓	✓	
Socialization/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioral††	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counseling‡‡	✓				✓	✓
Gynecologic and contraceptive services					✓	✓

22q11DS: Management and implementation of clinical guidelines
Available guidelines

- Full medical and neurocognitive assessment
- Safe sex, contraception, genetic counselling
- Internet safety
- Substance abuse
- Early detection of signs and symptoms of psychiatric illness

REVIEW | Genetics inMedicine

Practical guidelines for managing adults with 22q11.2 deletion syndrome

Wai Lun Alan Fung, MD, ScD[1–4], Nancy J. Butcher, MSc[2,5], Gregory Costain, PhD[2,5], Danielle M. Andrade, MD, MSc[1,6], Erik Boot, MD, PhD[1–4,7], Eva W.C. Chow, MD, FRCPC[2,4], Brian Chung, MRCPCH, MBBS[8], Cheryl Cytrynbaum, MS, CGC[9], Hanna Faghfoury, MD[10], Leona Fishman, MD, FRCPC[9], Sixto García-Miñaúr, MD[11], Susan George, MD, FRCPC[1,12,13], Anthony E. Lang, MD, FRCPC[6,14], Gabriela Repetto, MD[15], Andrea Shugar, MS, CGC[9], Candice Silversides, MD, FRCPC[1,16,17], Ann Swillen, PhD[18,19], Therese van Amelsvoort, MD, PhD[20], Donna M. McDonald-McGinn, MS, CGC[21–23] and Anne S. Bassett, MD, FRCPC[1–5,12,17]

22q11.2 Deletion syndrome (22q11.2DS) is the most common microdeletion syndrome in humans, estimated to affect up to 1 in 2,000 live births. Major features of this multisystem condition include congenital anomalies, developmental delay, and an array of early- and later-onset medical and psychiatric disorders. Advances in pediatric care ensure a growing population of adults managing the neuropsychiatric, endocrine, cardiovascular, reproductive, psychosocial, genetic counseling, and other issues that are the focus of attention in adults with 22q11.2DS. We propose practical strategies for the recognition, evaluation, surveillance, and management of the associated morbidities.

Initial assessment at diagnosis

- Full physical examination
- Genetic investigations and counselling
- Cardiac examination (EKG, echocardiogram)
- Assessment by palate team (SLT, palate surgeon, ENT) – If no concerns, by age 2 yrs
- Immunology investigations
- Neurology assessment (infancy) – Early intervention, physiotherapy
- Endocrine investigations
- Renal US
- Ophthalmological assessment – If no concerns, by age 3 yrs
- Refer for neurocognitive assessment at age 3-4 yrs (preschool education)
- Dentition and oral health
- Other specialists as needed

22q11DS: Management and implementation of clinical guidelines
Follow up

- General consultation/coordination of care:
  - Every 3-6 months first two years
  - Annually until age 6 years
  - Every 1-2 years thereafter
- Immunology, Endocrinology:
  - 3-6 months first two years, annually thereafter
- Cardiology, palate/speech, ophthalmology, other: as needed
- Psychology/Psychiatry: Assessment schedule, as needed

CHD diagnosed prenatally or shortly after birth

- Standard medical/surgical treatment
- Specific perioperative care (hypocalcaemia, immunological depression, bronchospasm, bleeding)
- Increased overall mortality
- Lifetime surveillance

No previous heart problems at diagnosis (any age)

- Full cardiac examination, management and follow up as needed

Women with 22q11DS and CHD who want to have a child

- Assess about risks for maternal, fetal and neonatal complications
- High-risk pregnancy to be managed in specialised hospital unit

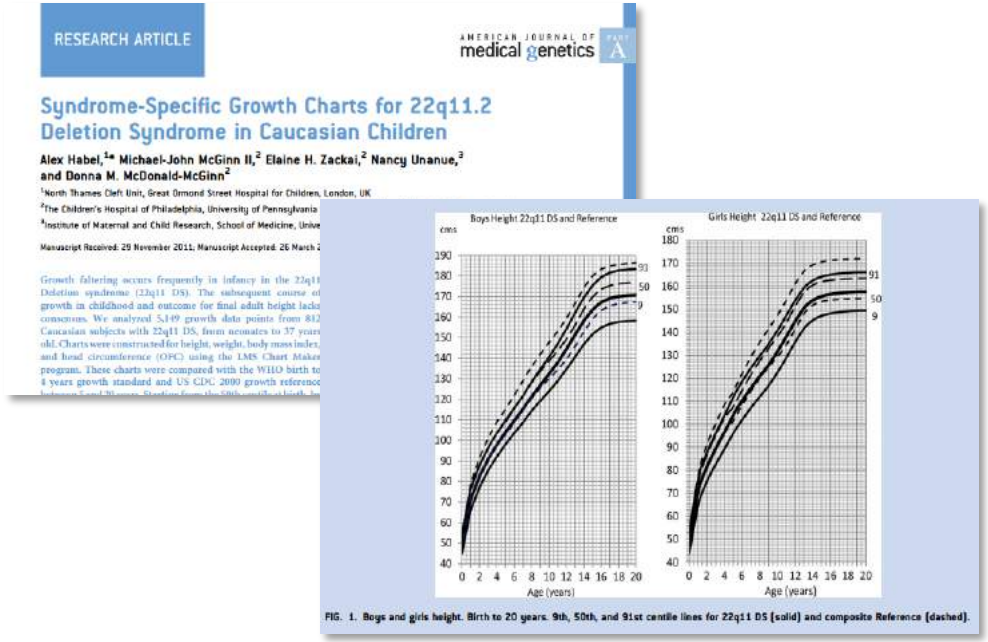
2. Palatal anomalies

- Joint team of palate surgeons, SLTs and ENTs with experience in 22q11DS
- Aware of peculiarities: increased depth of pharynx, hypodynamic palate
- Adenoidectomy may worsen VPI
- Overt cleft palate: Standard management, by first year of life
- Velopharyngeal insufficiency (VPI): Initial assessment of speech, individualized treatment plan, various techniques (no consensus), surgery usually performed at around 4-6 years of age.
- Additional considerations: Carotid medial displacement (MRI), cervical instability, perioperative calcium monitoring, postoperative sleep studies

3. Immune system disorders

- Usually mild immunodeficiency, improves by age 2-3 years
- Early assessment to provide guidance for live viral vaccines
- Regular follow up and assessment of immune response: Recurrent infections, response to vaccines, T cell count, Ig levels
- Ig treatment if antibody deficiency, antibiotic prophylaxis if recurrent infections
- Autoimmune disease (cytopenia, hypothyroidism, rheumatoid arthritis) managed with standard treatments, immunosuppression should be minimized
- Increased risk of allergies and celiac disease

- Early detection and of hypocalcaemia and thyroid dysfunction
- Special attention to calcium levels in neonatal period and at times of biological stress (surgery, puberty, pregnancy or delivery)
- Growth assessment, specific growth charts available, investigations as needed


RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Syndrome-Specific Growth Charts for 22q11.2 Deletion Syndrome in Caucasian Children

Alex Habel,[1]* Michael-John McGinn II,[2] Elaine H. Zackai,[2] Nancy Unanue,[3] and Donna M. McDonald-McGinn[2]

[1]North Thames Cleft Unit, Great Ormond Street Hospital for Children, London, UK
[2]The Children's Hospital of Philadelphia, University of Pennsylvania
[3]Institute of Maternal and Child Research, School of Medicine, Unive

Manuscript Received: 29 November 2011; Manuscript Accepted: 26 March 2

Growth faltering occurs frequently in infancy in the 22q11 Deletion syndrome (22q11 DS). The subsequent course of growth in childhood and outcome for final adult height lacks consensus. We analyzed 5,149 growth data points from 812 Caucasian subjects with 22q11 DS, from neonates to 37 years old. Charts were constructed for height, weight, body mass index, and head circumference (OFC) using the LMS Chart Maker program. These charts were compared with the WHO birth to 4 years growth standard and US CDC 2000 growth reference

Boys Height 22q11 DS and Reference

Girls Height 22q11 DS and Reference

cms

Age (years)

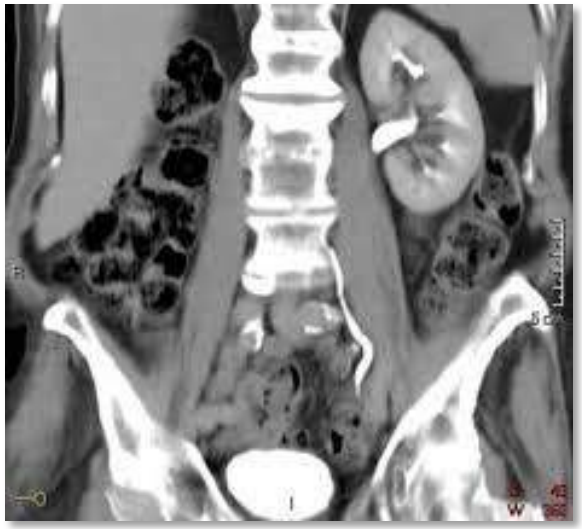
FIG. 1. Boys and girls height. Birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

5. Feeding and gastrointestinal disorders

- Early full assessment by SLT and/or GI specialists, identification of contributing factors
- Swallowing problems: X-ray barium contrast swallow
- Standard treatment for GER: Thickeners, anti-reflux measures, medication
- Feeding problems tend to improve by age 2 years
- If severe and failure to thrive, tube feeding or gastrostomy may be needed

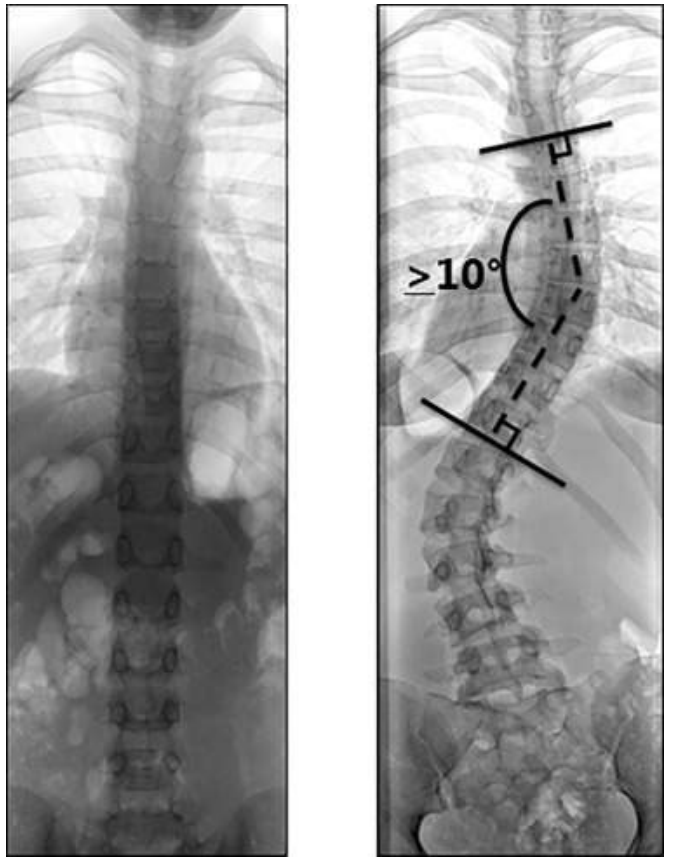
6. Genitourinary anomalies

- Physical examination and renal US at diagnosis
- Refer to specialist if needed
- (Risk of nephrocalcinosis secondary to calcium and vitamin D supplementation)



Scoliosis

- 15-45%, relatively mild, adolescent idiopathic scoliosis (1-4% population risk), with growth spurt
- 6-16% may need surgical treatment, increased surgical risk
- Screen for scoliosis during childhood and adolescence
- *(X-ray by age 9-10 years)*



(Homans et al. Medical Hypotheses 2019)

Cervical spine anomalies

- 46-90%, platybasia (flattening of skull base) and C1-C2 anomalies → instability, reduced spinal canal and cord dimension
- Unclear clinical consequences
- *(Flexion-extension X-ray at age 4-6 years)*
- Alert anaesthetists of the possibility of cervical spine injury with manipulating head and neck in unconscious child

Other

- Talipes equinovarus (clubfoot), polydactyly, etc.: Refer to specialist
- Joint laxity, leg pain

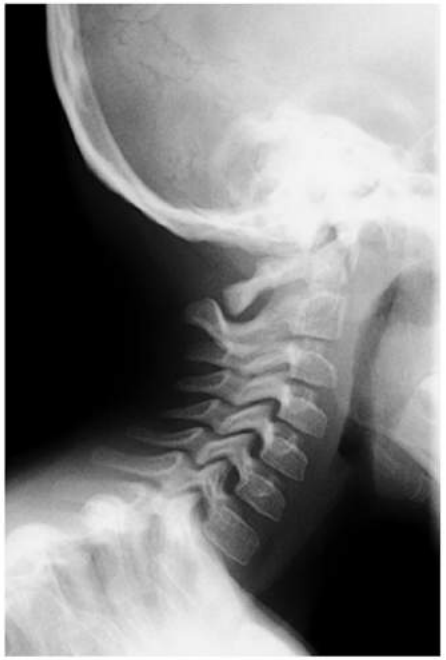


FIGURE 4 An 8-year-old child with 22q11DS and diagnosed with a C2 "Nike swoosh", which is an upswept lamina and posterior elements

(Homans et al. Am J Med Genet 2017)

8. Hearing and vision

Hearing

- Neonatal hearing screening (otoacoustic emissions)
- Request assessment if concerns, recurrent ear infections, speech delay, etc.

Vision

- Request assessment as needed: squint, concerns about sight, etc.
- Refractive errors (hypermetropia, astigmatism) are very common
- Ophthalmological examination at age 3 years

22q11DS: Management and implementation of clinical guidelines
9. Oral health

Acta Odontologica Scandinavica, 2012; 70: 194–201

informa
healthcare

ORIGINAL ARTICLE

Dental developmental disturbances in 50 individuals with the 22q11.2 deletion syndrome; relation to medical conditions?

HILDE NORDGARDEN[1], KARI LIMA[2,3,4], NINA SKOGEDAL[1], IVAR FØLLING[2], KARI STORHAUG[1] & TORE G. ABRAHAMSEN[4,5]

[1]*National Resource Centre for Oral Health in Rare Medical Conditions (TAKO-centre), Lovisenberg Diakonale Hospital, Oslo, Norway,* [2]*Department of Endocrinology, Division of Medicine, Akerhus University Hospital, Lørenskog, Norway,* [3]*Institute of Clinical Medicine, University of Oslo, Akershus University Hospital, Lørenskog, Norway,* [4]*Section for Pediatric Immunology and Infectious Diseases, Division of Pediatrics, Oslo University Hospital, Oslo, Norway, and* [5]*Faculty Division Rikshospitalet University Hospital, University of Oslo, Oslo, Norway*

- Tooth agenesis (15%), enamel hypoplasia (42%) and hypomineralisation (58%)
- Hypomineralisation twice as frequent in permanent teeth
- No correlation with clinical conditions (low calcium or PTH, infections, CHD, immune disease, VPI, prematurity, low birth weight)
- Regular contact with dental team

22q11DS: Management and implementation of clinical guidelines
10. Neurocognitive

TABLE 1 Treatment recommendations for improving neurodevelopmental outcome in 22q11 DS during infancy and early childhood (0–6y)

Developmental area	Developmental features	Treatment recommendations
Motor development	Hypotonia and neuromotor deficits	Physiotherapy, occupational therapy, and sensory integration therapy from early age on
Feeding	Poor sucking, nasal reflux, and oral motor coordination problems	Medical guidance/monitoring of feeding problems Feeding advice (feeding specialist with expertise in 22q11 DS)
Speech and language	Impaired speech and language development, hypernasality, high-pitched voice, and compensatory speech	Speech and language therapy, total communication approach (verbal, non-verbal, and sign language in combination with oral speech) (Solot et al., 2001) In the case of severe hypernasality, a pharyngoplasty is sometimes required
Neurodevelopment/ Cognitive development	Varying degree of impairment (from borderline development to mild–moderate ID)	Educational monitoring Early childhood specialist Anticipatory guidance
Social–emotional development and social skills	Emotionally reactive Problems with regulation of emotion and behavior Socially withdrawn, poor peer relations, self-directed behavior Social anxiety and general anxieties	Provide a secure and highly structured environment Infant mental health intervention Play therapy (structured play to promote social play) Structured (social) group experience
Attention	Easily distracted, impulsiveness	Structured (learning) environment Environment free from stimuli Use visual aids to improve sustained attention (sand timer; time-timer, etc.)

(Swillen et al. Am J Med Genet 2017)

Multidisciplinary clinic

- One hospital, same day
- Cases personally discussed between specialists
- Common database
- Includes transition to adult care
- Coordination with education and social services

Multidisciplinary clinic

- *Different hospitals*
- *Separate appointments*
- *Cases discussed between specialists* ***?***
- *Compatible databases*
- *Includes transition to adult care* ***?***
- *Coordination with education and social services* ***?***

In summary

- Multisystemic nature of disorder
- Multidisciplinary care by specialists knowledgeable about condition
- Coordinated by designated professional
- Guidelines available
- Individualised management plan
- Early detection and effective treatment of associated problems improves outcome
- Neurocognitive assessment from preschool age
- Need to improve transition to AND adult care
- Need to improve coordination with Education and Social Services

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