Syndromes at an older age

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Pitfalls in recognising the phenotype

- **Lack of medical information:** **-** poor data or no information on pregnancy/birth/early childhood
  - parents passed away; no contacts with family

- **Co morbidity influencing the phenotype:** the presence of more than one disease or medical condition at the same time.

  General: Cardiovascular problems, hypertension, cancer, diabetes, urine tract infection, dementia

  Specific: Vision and hearing problems, limitation of movements, epilepsy, speech difficulties, emotional problems, psychiatric problems, fractures, gastric and intestinal problems

- **Medication effects** (often long-term use)

- **Difficulties on recognizing the phenotype because of rare reports on clinical features in the older patient**

Co morbidity in older intellectual disabled patients

General

- **General**

- Cardiovascular problems
- Hypertension
- Cancer
- Diabetes
- Urine tract infection
- Dementia

- **Specific**

- Vision and hearing problems
- Limitation of movements
- Epilepsy
- Speech difficulties
- Emotional problems
- Psychiatric problems
- Fractures
- Gastric and intestinal problems

General aspects – medical problems (1)

- **Co morbidity**: the presence of more than one disease or medical condition at the same time.

- **Mental level**:
    * Not progressive (except for Down syndrome)
    * More serious level of intellectual disability:
        1. Higher risk for health problems
        2. Higher risk for specific problems (muscular-skeletal problems)
    * More often speech problems

General aspects – medical problems (2)

- **Orthopaedic problems**:
  * Progressive motor retardation
  * Fractures (females!!): resulting in:
    1. Discomfort
    2. Loss of independent functioning
    3. Complications due to inactivity

  * Hip fractures: high morbidity & mortality (12-20%)
    1. Seizures: no higher risk
    2. Use of medication: higher risk

General aspects – medical problems (3)

- **Gastro-intestinal problems**
  * Bedridden patients
  (reflux, gastric ulcer, constipation)
- **Cardiovascular problems**
- **Neurology**: epilepsy (relation with mental level)

- **Psychiatric problems**: emotional problems

General aspects – medical problems (4)

- **Ophthalmologic problems**: frequent
  * Mild-moderate ID: Landolt ring chart
  * Severe ID: Burghardt picture chart
  (distant vision)

- **Hearing problems**: frequent
  * Mild-moderate ID: play audiometry,
  speech audiometry, whisper test.
  * Severe-profound ID: free field audiometry

General aspects – behavioural problems

- **Severe-profound ID**:
  * Social contacts are limited (medical problems)
  * Difficulties with active communication result in aggressive behaviour and self-mutilation.

- **Mild-moderate ID**:
  * Periods of stress: inappropriate behaviour (excessive grief, introversion, avoidance)
  * Evolution to depression
    # Down syndrome
    # Difficult to diagnose
    # DD = hearing loss, hypothyroidism

List of syndromes

- 1. Angelman syndrome (del 15q11-13)
- 2. Cri du chat syndrome (5p deletion syndrome)
- 3. De Grouchy syndrome (18q deletion syndrome)
- 4. Down syndrome (trisomy 21)
- 5. Prader-Willi syndrome
- 6. Smith-Magenis syndrome
- 7. Velo-cardio-facial syndrome (22q11 deletion syndrome)
- 8. Williams-Beuren syndrome (7q11 deletion syndrome)

1. ANGELMAN SYNDROME

1. Angelman syndrome (AS)

1965: Harry Angelman, MD (1915-1996)

(Happy puppet syndrome)
Frequency: 1/10000 à 1/20000
Deletion chromosome 15

AS - Children

- Severe intellectual disability (ID)
- Microcephaly
- Epilepsy
- Broad based walking: spasticity, typical arm movements
- Typical facial features
- Periods of inappropriate laughter
- No speech, feeding difficulties
- Sleeping difficulties

AS - Adults

- Obesity
- Decreased mobility
- Scoliosis, kyphosis
- Seizures
- Keratoconus

AS – Medical problems (1)

- Microcephaly
- Short stature
- Atypical face and coarsening of the face
- Absent speech
- Changes in day-night rhythm

AS – Medical problems (2)

- Thoracic scoliosis (females)
- Decreased mobility
- Brachytelephalangy
- Epilepsy/seizures
- Severe neurological complications:
  - Severe tremor
  - Coordination problems
  - Spasticity

Clinical features > < genetic cause

- Deletion chromosome 15 (70%): classical features: microcephaly, motor problems, seizures, speech retardation
- UPD: uniparental disomy (pat) (7%): mild features: less frequent microcephaly, motor problems, ataxia, seizures
- Imprinting center defect (3%): less frequent microcephaly, motor problems, ataxia, seizures, improved speech
- UBE3A mutation (10%): seizures, intellectual disability

AS - Behaviour

- **Children**
  Hyperactive (actors)
  Interested in persons

- **General:**
  Behavioural problems in environment with poor variation (self-mutilation, mildly aggressive)

- **Adults**
  Passive (people-watchers)
  Interested in persons
  Social, impatient
  Easily to distract

- **Stereotypical movements:**
  "Mouthing" (hands-material)

AS – Differential diagnosis

- Complex diseases

  (Cerebral palsy, Lennox-Gastaut, autism, mitochondrial encephalopathy)

- Chromosomal abnormalities

  (22q13.3 terminal deletion, e.a.)

- Monogenic abnormalities

  (Rett syndrome, ATRX)

Problems in Angelman syndrome

- Medical
    * Coarse face
    * Scoliosis
    * Decreased mobility
    * Epilepsy
    * Changing day-night rhythm

- Behaviour
    * Hyperactive → Passive
    * Interested in persons

2. CRI DU CHAT SYNDROME

Cri du chat syndrome (CdCS)

- Deletion of the short arm of chromosome 5
  (5p deletion syndrome)

- Frequency: 1/40.000 - 1/50.000

- Critical region: 5p15 (Niebuhr, 1978)

- Zhang 2005:
  - *5p15.2-15.31: facial features
  - *5p15.31: high pitched cry
  - *5p15.32-15.33: speech retardation

CdCS (5p deletion) - Children

- High pitched cry
- Psychomotor retardation
- Microcephaly
- Craniofacial features:
  - Round face
  - Hypertelorism
  - Broad nasal bridge
  - Downward slanting palpebral fissures
  - Micrognathia

CdCS (5p deletion) - Adults

- ID
- Microcephaly
- Speech retardation
- Craniofacial features:
  - Long face
  - Large ears
  - Large mandible
  - Premature greying of the hairs
  - Macrostomia
- Scoliosis

CdCS - Behaviour

- General: Pleasant personality
- Childhood: Self-mutilation, head banging, scratching and biting, cruel to others
- Adults: Teasing, hyperactivity, periods of destructive behaviour, periods of aggression because of communication problems

Problems in CdCS

- Medical
  - * Scoliosis
  - * Feeding problems

- Behaviour
  - * Hyperactivity
  - * Teasing
  - * Pleasant personality
  - * Periods of inappropriate behaviour

3. DE GROUCHY SYNDROME

3. De Grouchy syndrome or 18q deletion syndrome

- ID / learning disabilities
- Short stature
- Facial dysmorphism: microcephaly, mid-facial hypoplasia, prominent antihelixes, low set ears
- Hearing impairment, narrow, atretic or stenotic external auditory canals, abnormalities of the middle and inner ear (atresia)

(Critical region CAA : 18q22.3-18q23)

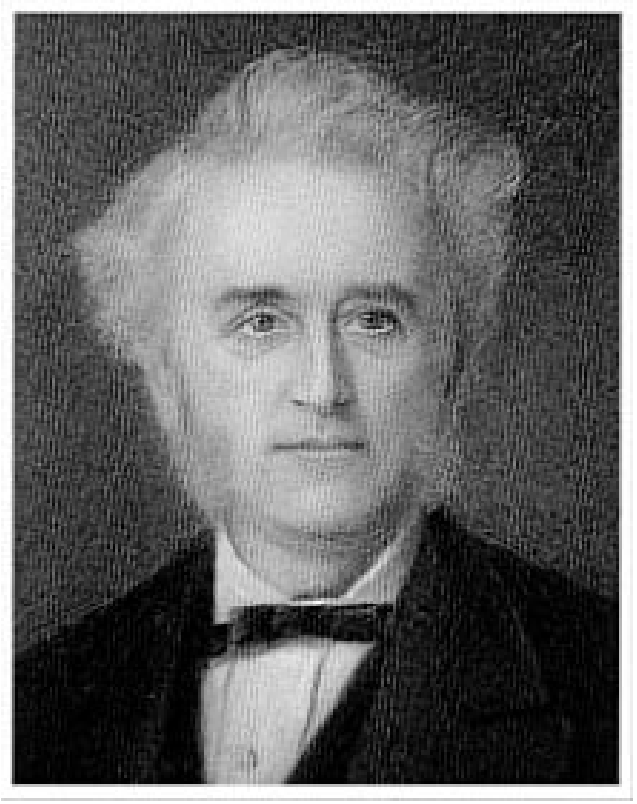
De Grouchy syndrome or 18q deletion syndrome

- Long tapering fingers, foot deformities
- Neurological problems: hypotonia, incoordination, tremor, seizures
- MRI: abnormal myelinisation

4. DOWN SYNDROME

Numerical abnormalities: Down syndrome

1866: Dr. JH Langdon Down

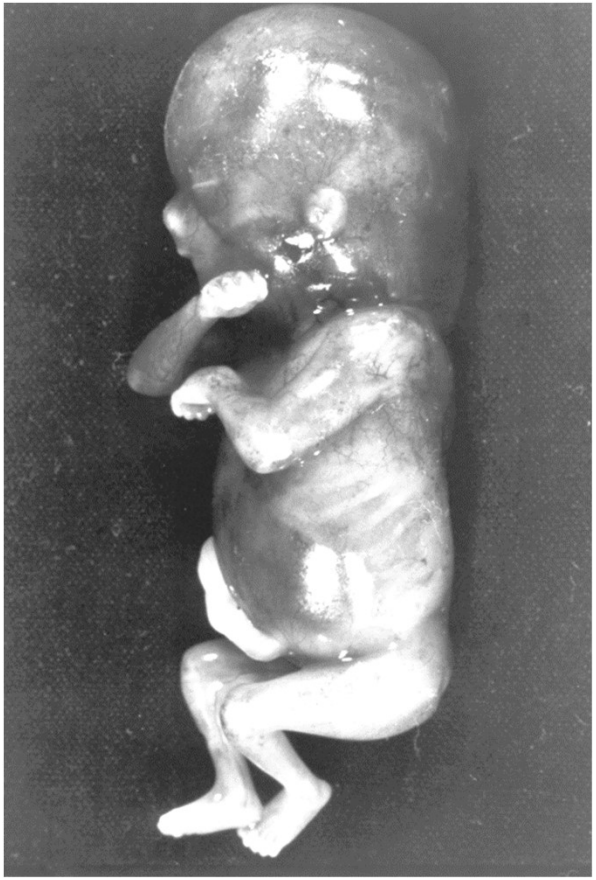


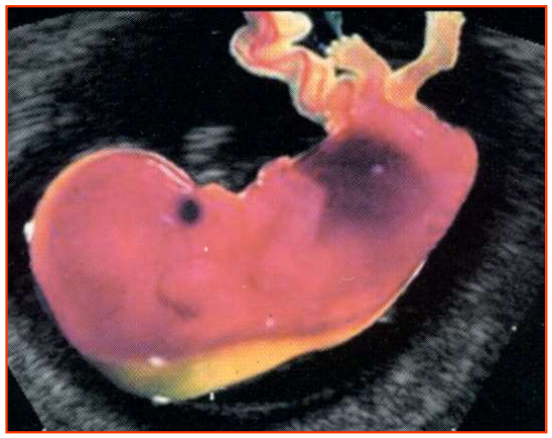
'In trisomy 21 , the skin appears
to be too large for the body'

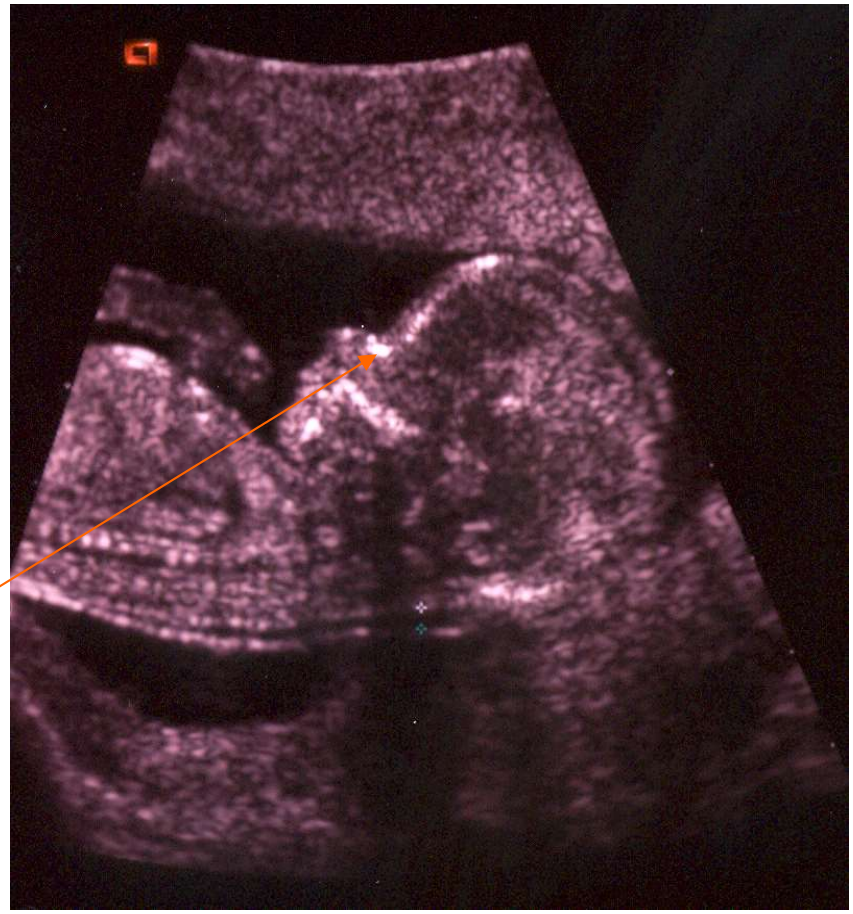
1959: Lejeune: extra chromosome 21

DS - Clinical aspects - Prenatal ultrasound

Nuchal Translucency: 11-13 6/7w







Foetal nasal bone

DS - Clinical aspects - Neonatal

Abundant nuchal skin

Brachycephaly

Upward slanting palpebral fissures

Protrusion of the tongue (hypotonic)

Epicanthic folds

Brushfield spots

Simian creases (1 or 2 hands)

Clinodactyly 5th finger

Hyperextensible joints

Hypotonic

Sandal gap, deep plantar crease

- **Difficult to recognise in newborn (especially when premature born)!**

DS- Clinical aspects – craniofacial features

Upward slanting palpebral fissures

Narrow ear canals

Flat face

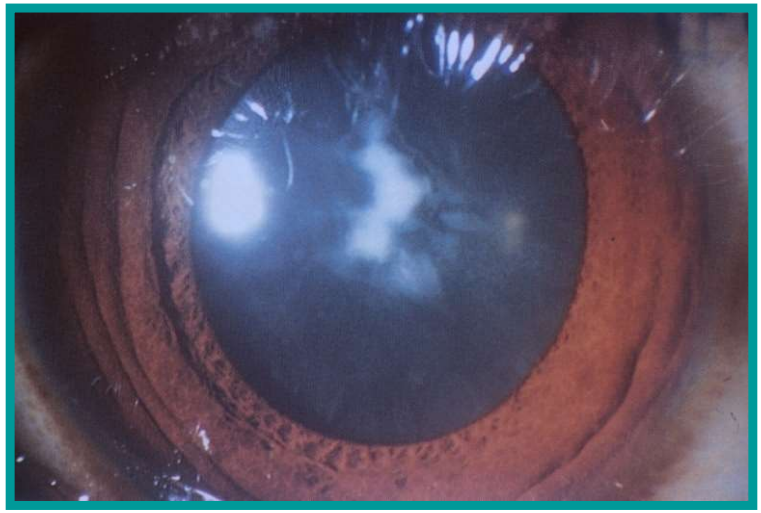
Large tongue

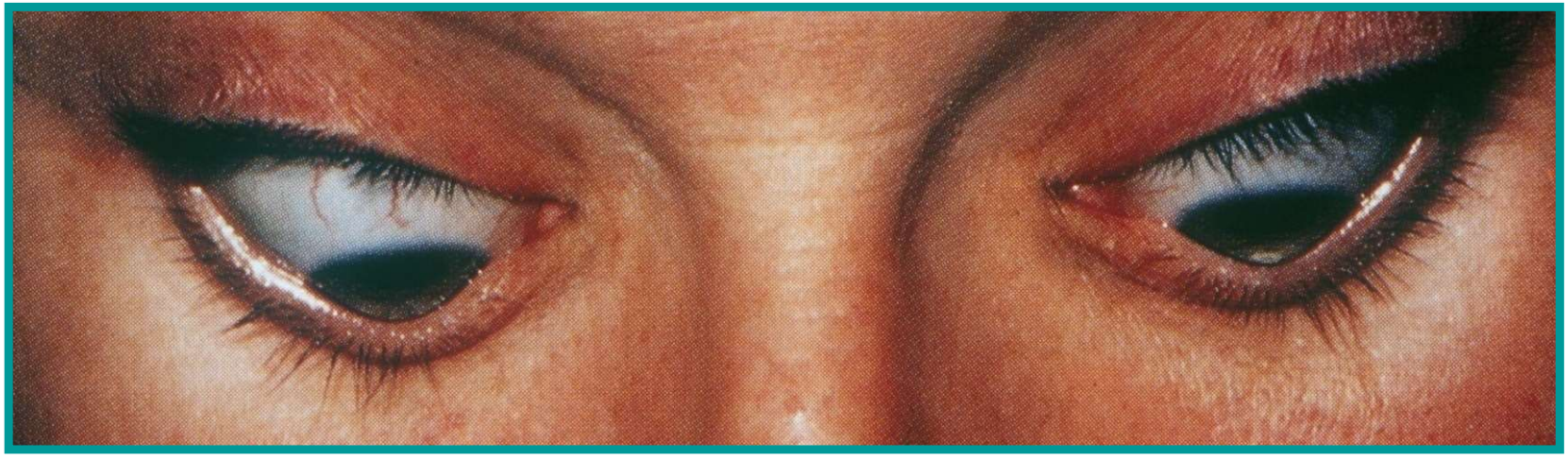
DS – Clinical aspects - General

- Growth: feeding problems
  short stature
  obesity
- Laxity of the skin
- Inguinal hernia
- Dry skin, alopecia, rash

DS – Facial - Eyes

Myopia (5-50%) (24.6%)
Astigmatism (70%)
Strabism (40-70%)
Blepharitis (2-46%)
Cataracts (9-17%) (40%)
Keratoconus (5-15) (17%)





DS – Facial - Ears

- Narrow ear canals (53%)
- Chronic otitis (40-60%)
- Cholesteatoma
- Presbyacusis

- Mixed hearing loss: 45%
- Perceptive hearing loss: 43.8%
- Conductive hearing loss: 10%

DS – Facial - Other

- **Nose:** sinusitis
- **Mouth:** teeth abnormalities (23-47%), periodontal disease (90%), sleep apnoea (31%), large tongue

DS - Cardiac - Pulmonary

- Cardiac problems (40-50%)
- Heart failure
- Pulmonary hypertension
- Respiratory infections: more frequent and serious

DS - Gastro-intestinal and immunologic system

- Neonatal icterus (60%)
- Anal stenosis
- Constipation (30%)
- Gastro-intestinal abnormalities (10-18%)
- Gastro-oesophageal reflux
- Celiac disease

- Hypothyroidism (22-40%)
  (Subclinical hypothyroidism)
- Diabetes type 1
- Frequent infections (12 times higher risk)
- Leukaemia (10 to 20 times higher risk)

DS - Orthopaedic

- Cranial: microcephaly, brachycephaly
- Axial: (occipito-) atlanto-axial instability (2-5%)
- Extremities: luxation of femur epiphysis, arthritis, joint dislocations

DS – Urogenital system

- Cystitis
- Renal problems
- Cryptorchidism (14-27%)
- Micropenis
- Infertility

DS - Neurological

- **CNS:** early ageing, dementia (Alzheimer)

- **Motor:** hypotonia, motor retardation, hypotonic muscles of mouth

DS – Behavioural phenotype

- ID: moderate to severe
- Speech problems: rough voice, poor articulation, retardation of the active speech

- Behavioural problems:
    * hyperactivity
    * obsessive behaviour
    * depression, anxiety

DS – Behavioural development

- Newborn: Passive

- Childhood : happy, stubborn and temper tantrums, difficult to manage, affectionate, hyperactivity

- Adolescent and adult: friendly, humoristic, compulsive

  Emotional problems: higher risk to depression

  R/ Psychotherapy and medication

DS - Dementia - Epilepsy

- **Dementia**: 18/96 (18.8%)

  *Age: increases with age
  40-49 y: 4 (11.1%)
  50-59 y: 14 (42.4%)
  *Important factor for (limited) prognosis

- **Epilepsy**: 16/96

  * 9 patients developed dementia
  * Present in 50% of the patients with Alzheimer dementia
  * One of the first signs of Alzheimer dementia

DS- Medical check list

1. Dementia
   * Cave epilepsy
   * Limited prognosis
2. Visual problems
   * Evaluation at least each 2 years
3. Hearing problems
   * Evaluation at least each 2 years

   Differential diagnosis:
   Dementia-Depression-Behavioural problems
4. Thyroid problems
   * Yearly screening

DS - Recommendations

- Yearly screening of residential adults:
    1. Clinical examination (heart auscultation)
    2. Thyroid function
    3. Examination of the eyes
    4. Examination of the ears
    5. Cognitive functioning and dementia:

- 1. Exclude medical and psychiatric causes
- 2. Questionnaires:

  * Daily Living Skills

  * The Dementia questionnaire for Mentally Retarded persons

  * Observation list for Ageing Residents

5. PRADER-WILLI SYNDROME

PWS – Frequency and genetics

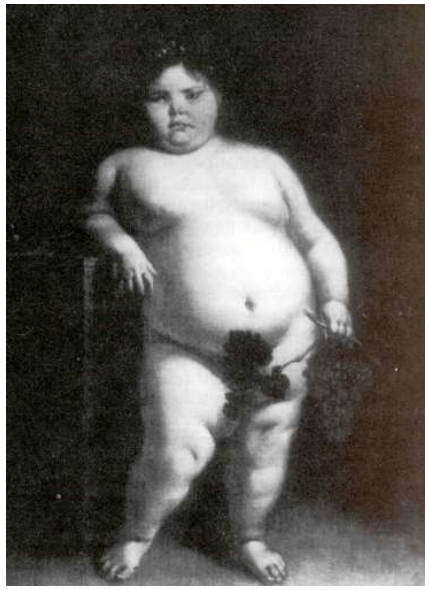
- Incidence: 1/30.000

- Genetics:

* deletion of the long arm of chromosome 15q11-13: 75%

* uniparental maternal disomy: 24%

* imprinting centre defects: <1%



PWS – Clinical features - General

- Hypotonic
- Obesity
- Mental retardation
- Genitalia poorly developed

PWS - Hypotonia

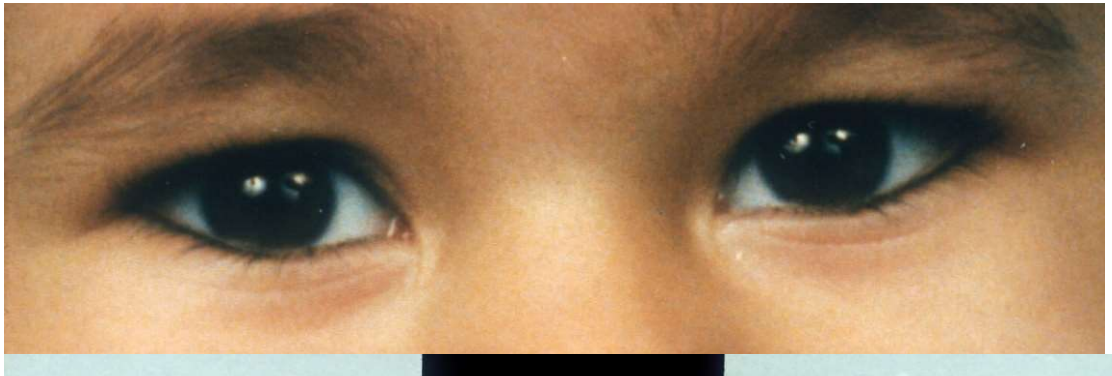
- Pregnancy:
  - * poor fetal movements
  - * polyhydramnion
- Birth:
  - *absent swallowing and sucking
  - * feeding problems
  - * weak cry
  - * heart- and lung problems
- First year:
  - * severe psychomotor retardation

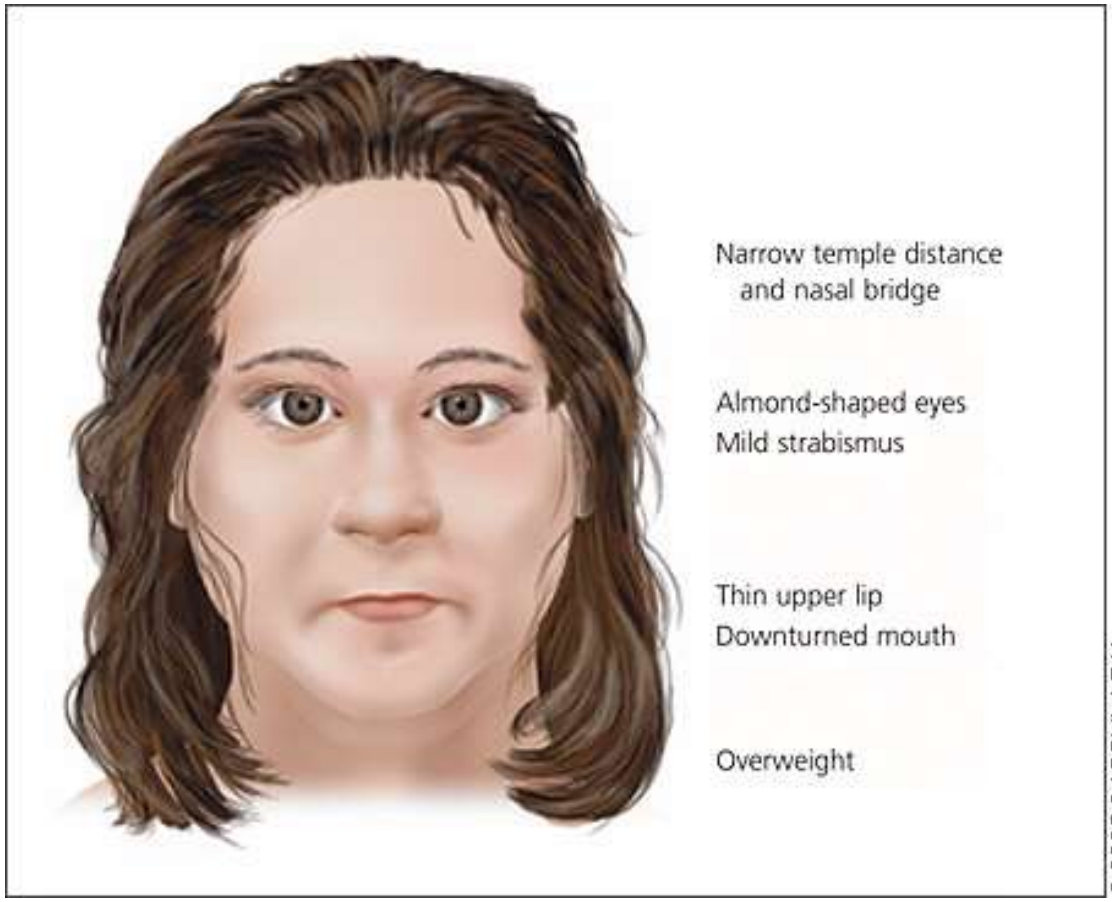
PWS - Intelligence

- Mean IQ 62
- 11% normal
- 23% borderline
- 26% mild mental retardation
- 26% moderate mental retardation
- 11% severe mental retardation

PWS – Facial features

- Narrow forehead
- Almond shaped eyes
- Micrognathia
- Tented mouth and thin upper lip
- Hypo pigmentation of the skin, hair and eyes





PWS - obesity

- Excessive appetite
- Decreased satisfaction
- Lower need to calories (energy)
- Inactivity

PWS – Hypothalamus

- Induction of birth
- Eating (Oxytocin): excessively
- Growth (GHRH): deficiency
- Drinking (vasopressin)
- Reproductive system (LHRH hormones): deficiency
- Rhythm: changed day-night rhythm
- Temperature system: disturbed
- Decreased sensibility to pain

PWS – Behavioural phenotype

- Motor retardation
- Intelligence: borderline (rare) to mild-moderate ID
- Obsession for food
- Obsessive-compulsive behaviour
- Skin scratching
- 10% of the adult PWS patients develop severe psychiatric problems (cyclic psychosis)

PWS - Recommendations

- Early intervention :(physiotherapy, diet and intervention of the behaviour)

- Structured environment
- Clear directions and supervision regarding feeding
- Psychiatric support
- Adaptation in the environment and drug therapy
- Avoid stressful situations
- Long-term follow-up!

6. SMITH-MAGENIS SYNDROME

SMS – Clinical findings – Children (1)

- Moderate ID
- Brachycephaly
- Coarse face:
  - Frontal bossing
  - Midfacial hypoplasia
  - Broad nasal bridge
  - Upper lip: tented mouth

SMS – Clinical findings – Children (2)

- Hoarse voice, explosive speech
- Short stature, broad thorax
- Broad hands
- Eye problems: strabismus, myopia
- Hearing problems: otitis media in childhood, hearing loss

- Decreased sensibility to pain
- Obesity, increased level of cholesterol

SMS: Clinical features (3)

- Reflexes weak
- Sleep disturbances
- Epilepsy
- Renal and urinary tract infections
- Scoliosis
- (Rarely: congenital heart diseases and renal abnormalities)

SMS - Clinical findings – Adolescents -Young adults

- Mild-moderate-severe ID
- Brachycephaly
- Coarse face: prognathia
- Midfacial hypoplasia
- Upper lip: tented mouth
- Small ears
- Hoarse voice, explosive speech
- Short broad hands

SMS – Changing clinical features with age

- Scoliosis
- Obesity
- Eye problems: myopia
- General aspect: small stature, broad thorax
- Facial coarsening: prognathia

SMS - Clinical differential diagnosis – age-related

- **Newborn:** Down syndrome (facial dysmorphism and hypotonic)

- **Toddlers:** MPS (coarse face)

- **Children:** 1. Prader-Willi syndrome (hypotonic, hyperphagia, SS, behaviour)

  2. Fragile X syndrome (attention deficit)

- **Adults:** Fragile X syndrome (prognathia)

SMS - Behaviour - Children (1)

- Gentle, attractive, very sociable and appealing smiles

BUT easily upset:

- Difficult behaviour: temper tantrums, ADHD
- Inappropriate social behaviour: too familiar with strangers
- Demanding
- Ambivalent
- Sleeping problems
- Autistic-like (some toddlers)

SMS - Behaviour - Children (2)

- Stereotypic behaviour: hand licking, mouthing, rocking, special fascination for objects or faces

- Self-mutilation

  Head banging, hitting, biting

SMS - Behaviour – Adolescents – Young adults

- Very sociable
- Hyperactive
- Poor attention
- Sleeping problems
- Stereotypic behaviour: hand wringing and arm-clasping (self hugging)
- Self-mutilation: nail yanking, scratching, skin picking, inserting objects or fingers into body orifices

SMS: Cognitive profile and behavioural problems

- ID, moderately
- Visual-perception skills > auditory perception skills
- Poor verbal skills

- Behaviour problems: difficult, aggressive, self mutilation, stereotypic behaviour, severe sleeping problems

(are not diagnosed or recognised with questionnaires!)

SMS – Recommendations

- **Medical follow-up:**
  - Scoliosis
  - Obesity
  - Eye problems

- **Behaviour:**
  - Sleeping problems
  - Demanding and ambivalent behaviour
  - Hyperactivity
  - Stereotypic behaviour
  - Self mutilation: avoid frustration

7. VELO-CARDIO-FACIAL SYNDROME

Velo-cardio-facial syndrome

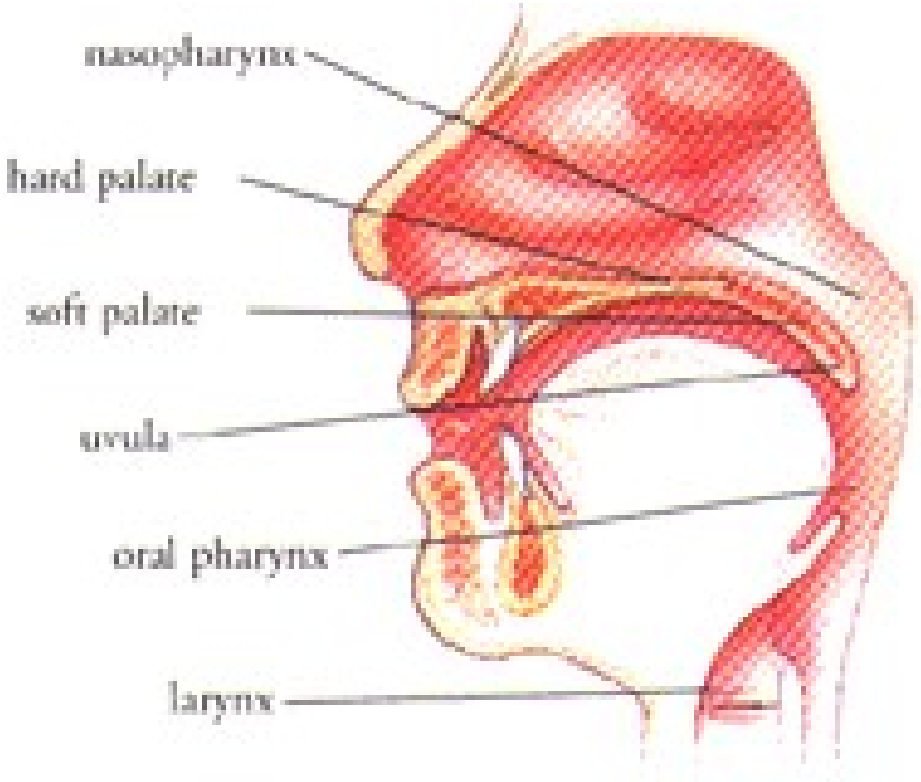
Velo:	pharyngeal problems, feeding problems and nasal speech
Cardio:	conotruncal heart anomalies (ToF) (50-75%)
Facial:	typical long nose, broad nasal bridge, small mouth small chin low-set ears, relatively small head circumference

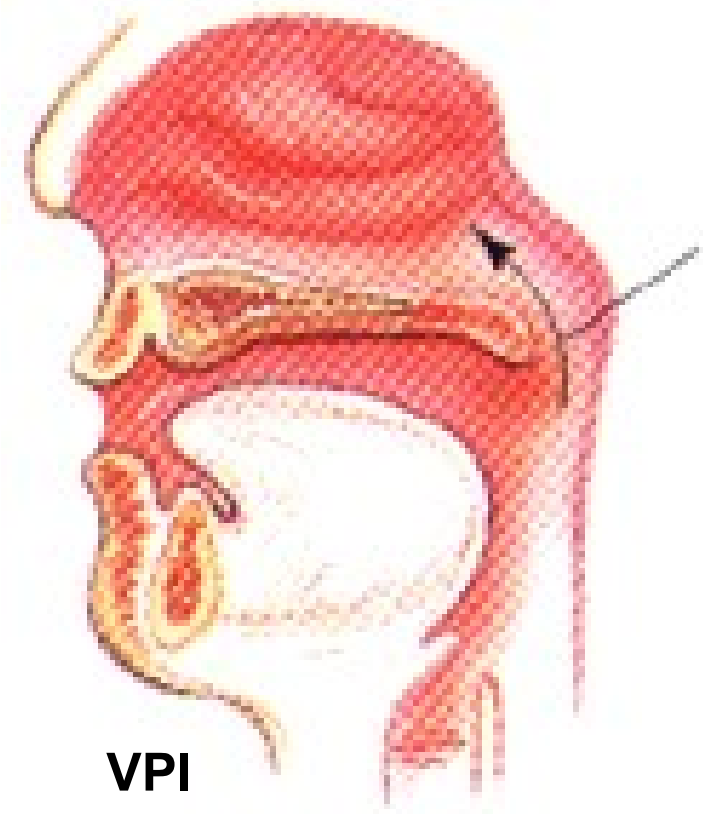
Hypotonia

Paryngeal

- 2% cleft
- 88% velopharyngeal insufficience

due to submucuous pharyngeal cleft





VPI

- Prenatal : polyhydramnios
- Neonatal : feeding difficulties

  - feeding takes a long time

    (no breastfeeding)

  - nasal reflux

  - bifid uvula

Velopharyngeal abnormalities

* Neonatal feeding difficulties

* Young children
  - recurrent middle ear infections
    (avoid adenoidectomy !!)
  - delayed speech development
  - articulation problems, hypernasality
    (also at older age)

Cardiac problems

- Children with del22q11 : 50-75% cardiopathy
- Type? (**Momma** et al., Am J Cardiol 1996 – 100 patients)

  73% Tetralogy of Fallot,
  12% VSD
  5% aortic arch abnormalities (without intracardial abn)
  4% interrupted aortic arch (type B)
  2% DORV
  2% truncus arteriosus,
  1% transposition
  1% ASD

Hypocalcemia

- Hypo- or aplasia parathyroids
- Presents as convulsions during the first weeks of life
- Treatment

  - symptomatic ?

  - Be aware for overtreatment => nefrocalcinosis
- Not permanent (temporarely)
- Monitoring calcium in premature neonate or postoperatively

Facial features

typical long nose,

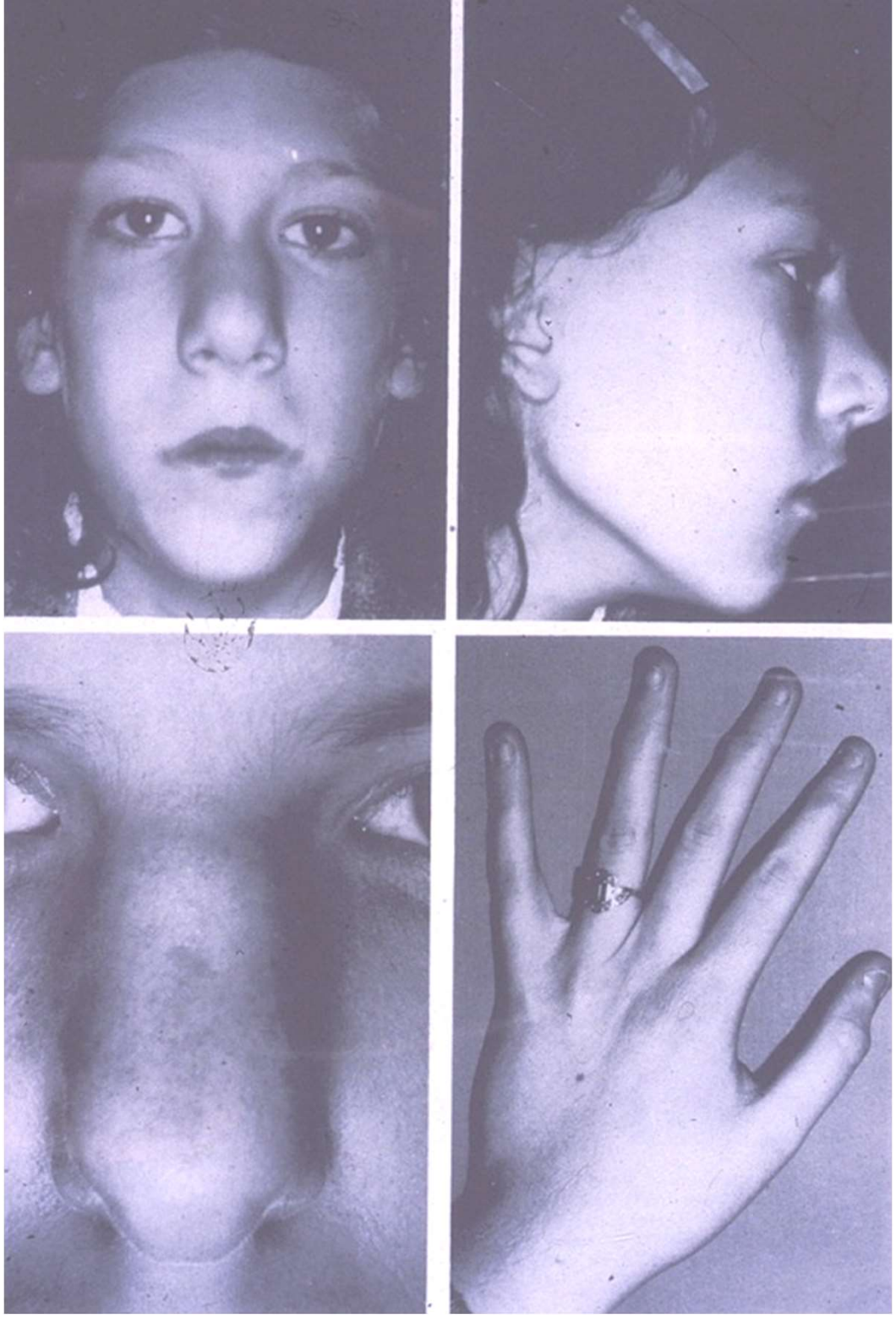
broad nasal bridge,

small mouth

small chin

low-set ears,

relatively small head circumference



8. WILLIAMS-BEUREN SYNDROME

WBS – frequency - genetics

- 1 / 20 000
- Boys = girls

- Microdeletion of chromosome 7(q11.23)
    * Elastin gene
    * several other genes

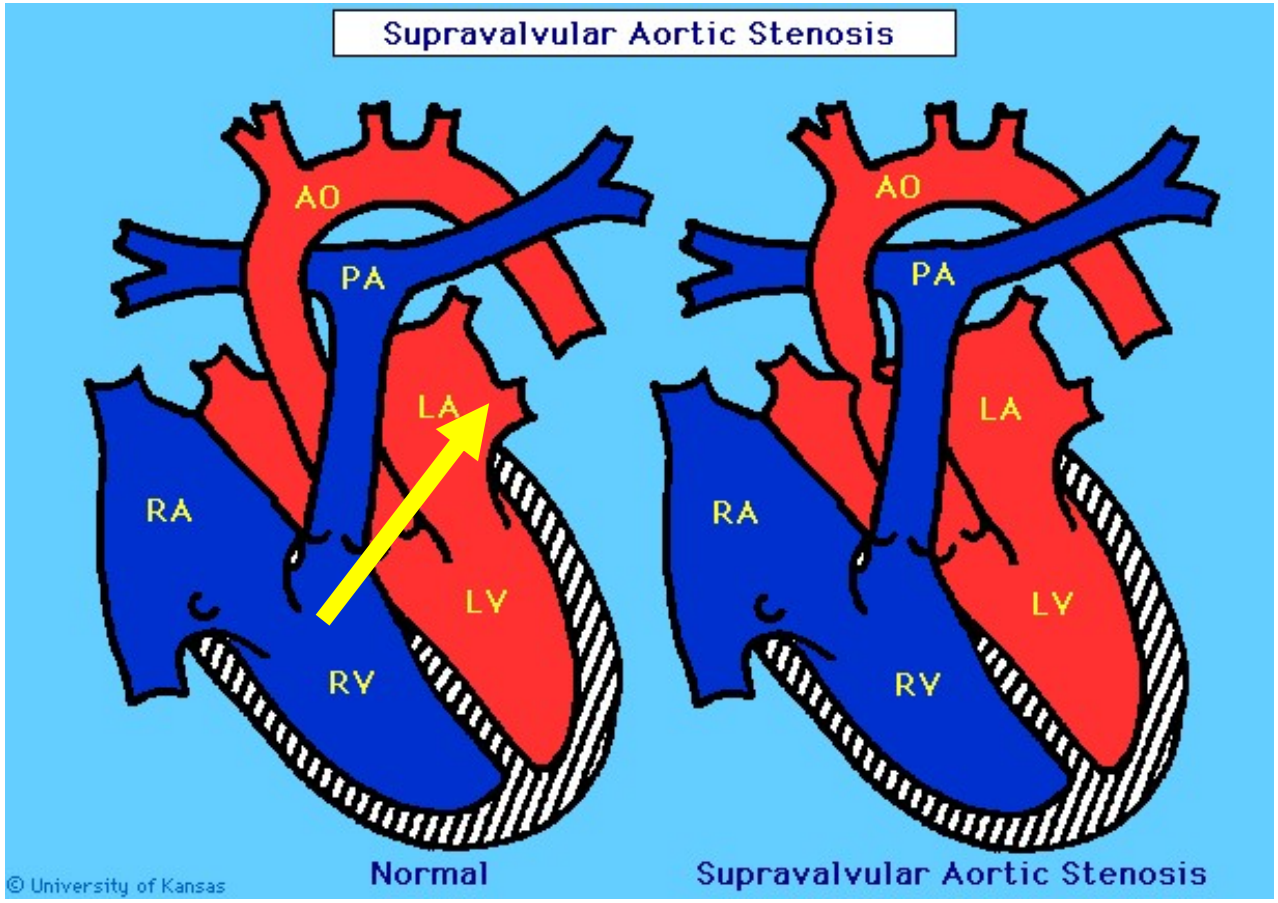
- Diagnosis: FISH-studies and CGH (micro-array)

WBS – facial features

- Broad forehead
- Full eyelashes
- Strabismus
- Iris stellata
- Broad nasal bridge
- Full cheeks
- Broad mouth and full lips

WBS – cardiac features

- Supra-valvulair aorta stenosis
- Peripheral pulmonary stenosis



WBS - General

- Newborn: elevated calcium level in blood and urine
- Growth retardation
- Hyperacusis
- Teeth abnormalities

WBS – Cognition and behaviour

- Psychomotor retardation
- Moderate to severe learning problems
- Relatively good developed speech
- Social personality
- Concentration problems and easy to distract

WBS – Medical check list –multidisciplinary approach

- Blood pressure
- Urine-investigation (calciuria)
- Physical examination:
    - ! Bones and joints
    - ! Posture
- Eye examination
- Dental problems

Importance of a diagnosis in ageing intellectually disabled persons?

- Patient
  - Recognition of comorbidity
  - Behavioural guidance and therapy
- Family
  - Genetic counselling – risk evaluation (prenatal setting)
- Institution (residential setting)
  - Setting adaptation in function of the medical and behavioural problems

Frailty

Frailty is a common clinical syndrome (= group of symptoms that characterize a specific condition) in the elderly population.

In its simplest form, it is a state of vulnerability to adverse occurrences.

Therefore, small disruptions may turn into important health problems.

Frailty increases the risk for disability after an incident, accidental falls or hospitalization.

The identification of people at high risk is needed to prevent and treat frailty efficiently.

Sciensano.be
Schoufour J et al 2016

Conclusion: older mentally retarded persons:

* Clinical data: difficult to obtain in the group of older patients

* Clinical examination:

recognizing the phenotype may be difficult:

- ageing: coarsening facial features
- influence of medication (often intake during a long time)

* Technical investigation:

- FMR-1 (females !!)
- Molecular cytogenetics (micro-arrays-exome): difficulties in interpreting results when no parents available (deceased).
- (metabolic testing)

Current problems:

* Clinical data (difficult to obtain in the group of older patients)

* Clinical fenotype recognition may be difficult: changing fenotype with age

* Behavioural fenotype not always well known

* Interpreting the results of genetic testing (no parents available - deceased)

Future aspects:

- Recognition of the (behavioural) phenotype may change because of intensive medical follow-up and guidance from early childhood on. (→ influencing the “natural” phenotype) (e.g. growth hormone therapy in Prader-Willi syndrome)

- As patients will survive longer → other problems will arise (Psychiatrical? Medical?).

- Cooperation with family support groups remains important

Thank you!