CHARGE syndrome -

medical diagnostic information and health challenges

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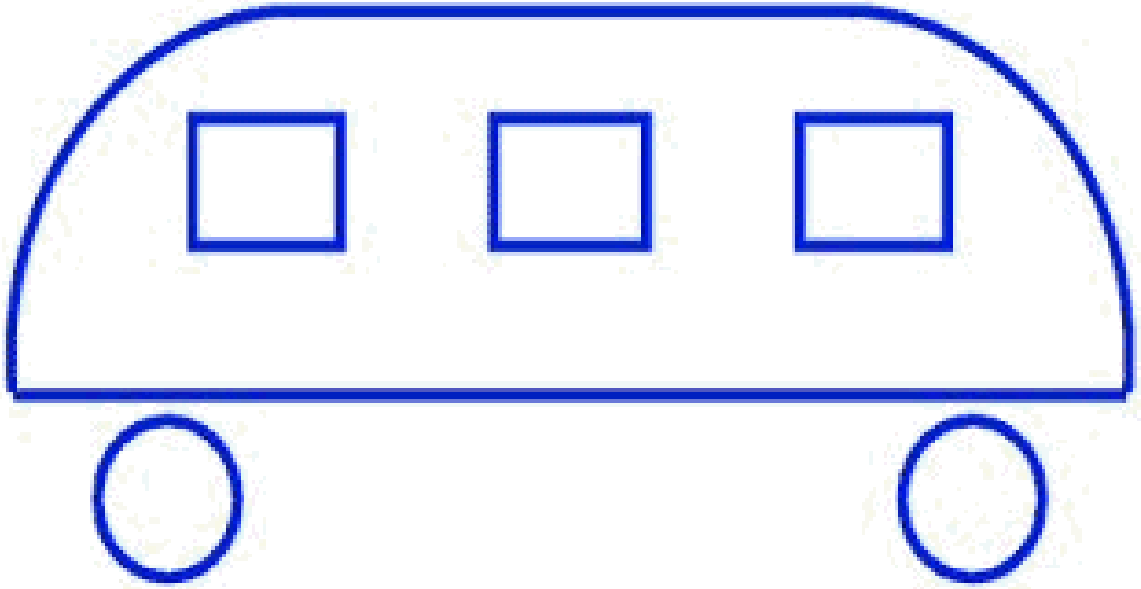
FRAMBU
KOMPETANSESENTER FOR SJELDNE DIAGNOSER

Plan for the presentation

- Introduction to the rare field
- Challenges to the «system»
- The way to a diagnosis
- Background
- History
- CHARGE
- Combined sensory loss
- Follow-up

Test



What is rare?

- When less than 100 persons per 1 million inhabitants , i.e. 1 : 10 000, have the same condition/syndrome/disorder/disease/diagnosis, it is defined as rare.
- In Norway this means less than 500 persons are affected by the same thing.
- It is estimated that there are 30 000 (?) people living with a rare diagnosis in Norway;
  30 million in Europe (with a less strict definition i.e. 5 : 10 000).

- There is an estimate of 6000-8000 different rare diagnoses.

Eurordis: What is a rare disease?

- **Key figures**
- **A disease or disorder is defined as rare in Europe when it affects fewer than 1 in 2000.**
- A disease or disorder is defined as rare in the USA when it affects fewer than 200,000 Americans at any given time.
- One rare disease may affect only a handful of patients in the EU (European Union), and another may touch as many as 245,000. In the EU, as many as 30 million people may be affected by one of over 6000 existing rare diseases.
- 80% of rare diseases have identified genetic origins whilst others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative.
- 50% of rare diseases affect children.

Concepts and explanations

How do you explain what you have?

- **State/Condition**: Something which is acute, transitory or permanent, more or less… , and can be due to lots of causes.
- **Disorder**: Sometihing which tends to be for ever, i.e. chronic.
- **Symptom**: Sign or feature of a disease or a syndrome
- **Syndrome**: Two or more symptoms, traits or findings that tend to appear together at the same time and are thought to have the same cause.
- **Disease**: Physical or mental «inbalance» due to internal or external factors affecting an organ or the whole body.
- **Disability**: Reduced ability to do something
- **Chromosomal disorder/aberration/gene mutation:** Change in the «recipi book» that influences the «product» and affects the owner of it.
- **Diagnosis:** A label connected to a description of a disease, a disorder or a syndrome.

Challenges might be similar in several disorders and diagnoses:

- Variable and fluctuating level of function
- Reduced motor skills, coordination difficulties, unsteadyness
- Muscular hypotonia or hypertonia
- Feeding/eating problems, nutritional difficulties
- Disturbed sleeping pattern, reduced sleep
- Recurrent infections, fever, dysregulation of body temperature
- Congenital malformations (heart, brain, ear, gastro-intestinal, uro-genital, etc)
- Sensory defects (vision, hearing, tactile, joint sense, temperature sense)
- Difficulties in intergrating and interpreting sensory inputs
- Attacks, fits, seizures, epilepsy
- Speech and communication problems
- Concentration and attention
- Behaviour, hyperactivity, impulsivity,
- Disturbances in the autonomic nervous system

What can be done?

- Take the challenges seriously!
- Repeat investigations and assessments to explore for causes and functional diagnoses.
- **Delayed development or disturbed development**?
- **Descriptual diagnosis**: Headsize, MRI of the brain, scoliosis, epilepsy, etc.
- **Etiological diagnosis**: Based on the cause, like a chromosomal disorder, gene mutation, etc.
- **Functional diagnosis**: Problems and challenges connected to things or activities like eating, walking, learning, communication, etc.
- Investigate for other challenges described for the syndrome
- Prevent complications and reduce risks
- Remember **comorbidity**

Functional diagnosis

- A way of expanding the frame of understanding of persons with genetic syndromes and their specific and individual challenges.
- Pointing out areas to work with, rather than providing reasons for people to escape and defend themselves behind walls of ”there is nothing we can do”.
- Enabling professionals to take on responsibility in their field of expertice and skills
- Making everybody aware of the reality, as well as seeing the possibilities for training for improvement and activities for fun, rather than the limitations of development, and thereby adding quality to life.

Functional diagnosis:

- Based on what is difficult or troublesome for the person.

  The reason could be an intellectual disabillity/mental impairment, autistic specter disorder (ASD), a neurodevelopmental disturbance or disorder, or may be the person has an etiological diagnosis that does not fully explain why the person functions as he or she does.

  It could of course also be a question about comorbidity.

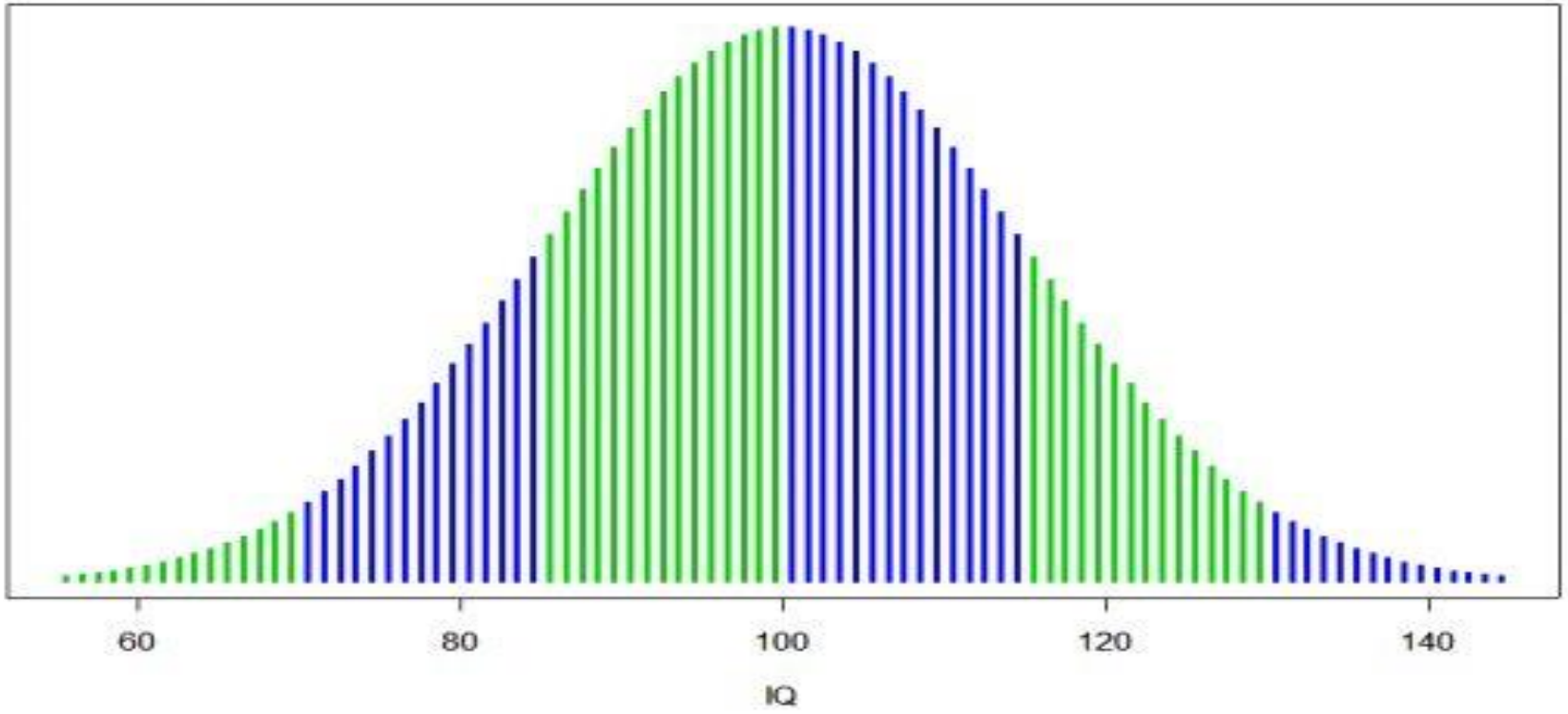
Classic autism or autistic specter disorder (ASD)

- Child autism: Profoundly disturbed development detectable before age 3 with abnormal function related to social interaction, communication and limited, stereotypic, repetitive behaviour.

  In addition often non-specific problems like disorders in eating, sleeping, fits of rage, self-destructive behaviour.

- Atypical autism: onset after 3 years of age.

- ASD: A wide range of different autistic traits and symptoms that may change with situation and age.



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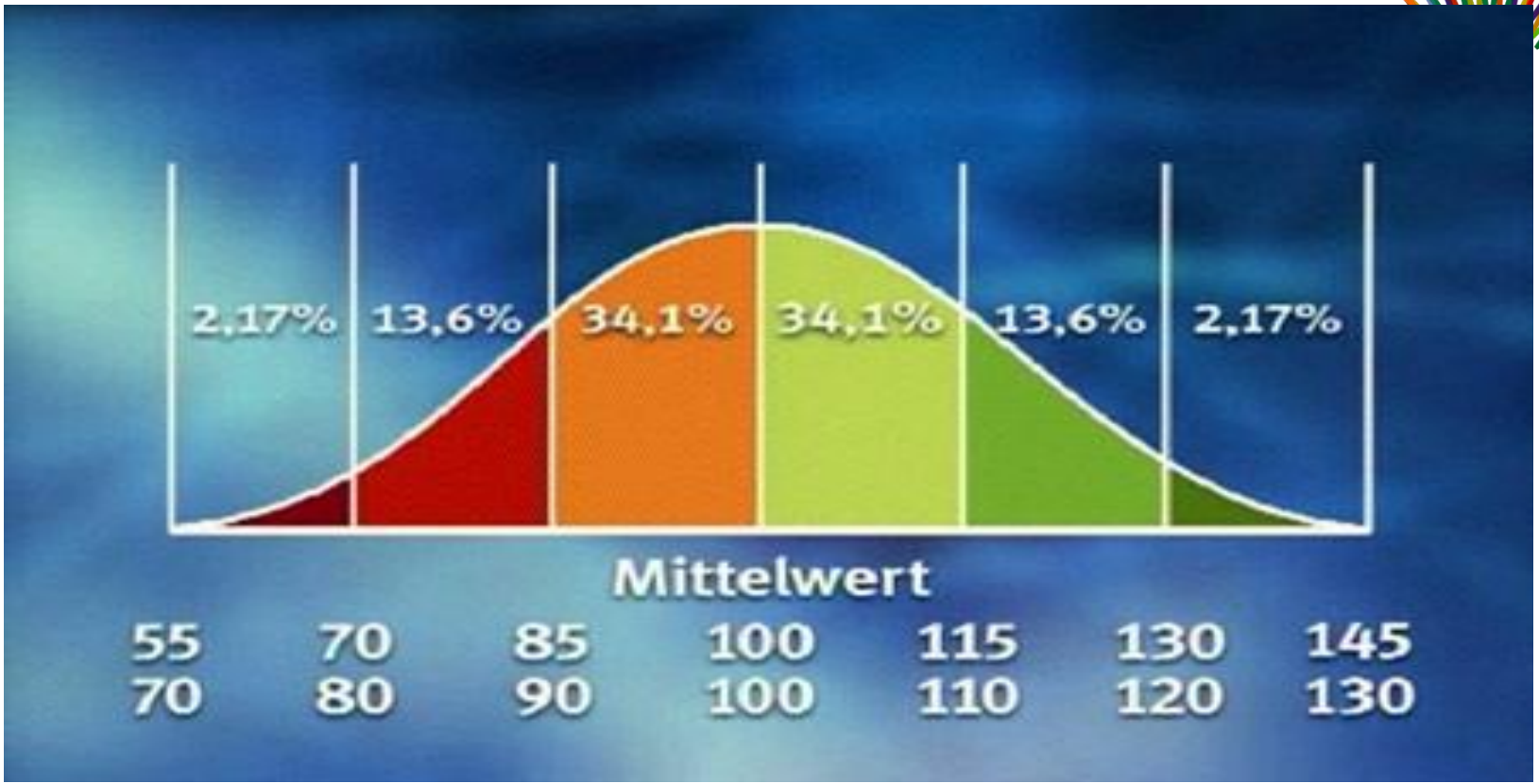


Bilde fra: foerderverein-der-europaschule-e-v.online.de

Diagnostic overview of Mental impairment (IQ< 70) (*intellectual disability)*:

Specified:

- Light; IQ: 50-69, (adults, mental age 9-12 years)
- Moderate; IQ: 35-49, (adults, mental age 6-9 years)
- Serious; IQ: 20-34, (adults, mental age 3-6 years)
- Profound; IQ below 20, (adults, mental age below 3 years)

Unspecified: Not testable (cooperatively or technically)

Comorbidity:

- Conditions or diseases that may occur or appear together with the main diagnosis or the disorder, but may have another cause, explanation or treatment.
- Many of the rare disorders at Frambu have plenty of comorbidities connected, that should be examined and investigated separately for what they add of extra burden of trouble and challenges, pain and concerns for the person affected.
- Some comorbidities may be avoided by raising awareness or by preventive measures.
- Many have options for treatment!

Airway distress is an example of common «everyday medicine» that may have many different causes:

- Mucus in the airways may be due to
  - Infection
  - Asthma or allergy
  - Gastro-oesophageal reflux
  - Autonomic nervous system disorder
  - Teeth grinding
  - Reduced muscular strength to cough it up
  - Others?

CHARGE syndrome

Historical background of CHARGE

- 1979: First clinical description (Hittner and Hall)
- 1981: Called «CHARGE association» (coloboma, congenital heart disease, choanal atresia with multiple anomalies)

- Unknown genetic cause for many years
- 2004: A Dutch group of researchers found changes on chromosome 8 (8q12.2): Chromodomain helicase DNA-binding protein-7 (CHD7-gene)
- Change of name to CHARGE syndrome (an acronyme/an initial word).
- CHD-protein important in fetal life (day 32-45) for the development of eyes, anterior parts of the brain, and structures involved in construction of the face, heart, kidneys etc.

What does CHARGE stand for?

C stands for Coloboma of eye (parts of eyes don't develop).

H stands for heart Defects.

A stands for Atresia of the Choanae (parts of nose don't develop).

R stands for retardation of growth/development.

G stands for genital abnormalities.

E stands for ear anomalies and or deafness.

CHARGE SYNDROME

- Still a clinical diagnostic entity
- Might be confirmed genetically by identification of CHD7-mutations or other changes on chromosome 8q12.2 in about 70% of cases.
- Occurs in 1 : 8500-17 000 live births;

  i.e. 4-6 new individuals every year in Norway?
- No difference in gender or ethnic origin
- By November 2017 Frambu has registered 15 persons (age 3-37 years, 9 females/6 males)
- How many persons with CHARGE syndrome do we know of in Norway?

CHARGE SYNDROME: A broad range of expressions

- A high degree of variation in burden of symptoms, pain and health issues
- Considerable differences in sensory loss and problems of perception and integration of input from the different senses
- Variation in motor functions and endurance
- A large span in cognitive functions and comprehension
- Large differences in skills of communication
- …and much more…

CHARGE: Medical follow-up and habilitation

- Individual adjustment
- Continuity: Follow-up over time
- Multidisciplinary approach and assessments by different specialists
- Interdisciplinary collaboration wanted and necessary
- Aim at compensation of sensory loss as much as possible
- Assess motor and cognitive (intellectual) abilities and capacities
- Focus on communication, social development and behaviour

The CHD7 gene

- Codes for CHD-7-protein that regulates macro molecules (chromatine/histones) that «wrap up» our DNA.
- A remodelling of chromatine will influence the expression og the gene in early parts of fetal life and development. This is called ***epigenetic etiology.***
- Different mutations in the CHD7-gene may cause different presentations and levels of severity of CHARGE.
- Changes (mutations) in the CHD7-gene are almost always spontanous and new:
  - 2-3 % recurrence risk (parents)
  - 50% risk (dominant transmission) for passing the mutated gene to the next generation if a person with CHARGE/CHD7-mutation gets children.

Types of CHD7 mutations

(Janssen et al., Hum Mutat.2012;33 (8):1149-60)

- Nonsense: 44%
- Frameshift: 34%
- Missense 8%: Milder cases
- Splice site: 11%
- Complete or partial deletion/duplication of CHD7: 2%
- Balanced chromosomal rearrangements: <1%

Diagnostic criteria for CHARGE syndrome

Blake's diagnostic criteria (1998)
(Blake K.D. et al., 1998; Clin Pediatr (Phila), 37(3):159-73)

Major criteria (4 C's)
Coloboma -of iris, retina, choroid, disc; microphthalmia
Choanal atresia
Cranial nerve (especially VII and VIII) dysfunction
Characteristic ear abnormalities

Minor criteria
Genital hypoplasia
Developmental delay
Cardiovascular malformations
Growth deficiency
Orofacial cleft
Tracheoesophageal fistula
Characteristic face

Occasional criteria
Renal anomalies
Hand anomalies
Abdominal defects
Spine anomalies
Neck/shoulder anomalies
Thymic/parathyroid hypoplasia

Diagnostic criteria interpretation

Definite CHARGE: 4 major or 3 major and 3 minor criteria
Probable/possible CHARGE: 1 or 2 major and several minor criteria

Verloes' diagnostic criteria (2005)
(Verloes A. 2005; Am J Med Genet A. 15;133A(3):306-8)

Major criteria (3 C's)
Coloboma (iris or choroid, with or without microphthalmia)
Choanal atresia
Hypoplastic semi-circular **C**anals

Minor criteria
Rhombencephalic dysfunction (brainstem dysfunctions, cranial nerve VII to XII palsies and neurosensory deafness)
Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin deficiencies)
Abnormal middle or external ear
Malformation of mediastinal organs (heart, esophagus)
Mental retardation

Diagnostic criteria interpretation

Typical CHARGE: 3 major, or 2 major and 2 minor criteria
Partial/incomplete CHARGE: 2 major and 1 minor criteria
Atypical CHARGE: 2 major, or 1 major and 3 minor criteria

Colobomas

- Slit or hole in the eye
  - Present in 70-80%
  - Visible or non-visible (most common)
  - Arises in 5th.-7th week of pregnancy
  - Incomplete closure of the primitive eye

Vision problems in CHARGE

- May be caused by abnormalities in the eye itself.
- OR: Caused by developmental changes of the perception or interpretation of light and vision signals.

- Hypersensitivity to light/photophobia
- The optic nerves may be affected
- Colobomas of the retina may cause loss of vision field or detachment/ablation of the retina
- Small eyes

Heart defects in CHARGE

- Common: 66-92%
- All types from small to large
- High incidence of serious types, conotruncal defects, meaning involvment of heart valves and walls separating the chambers of the heart

CHARGE and heart defects

- Association with:
  - Choanal atresia
  - Fistulas between the trachea and the esophagus
  - Often serious mutations of the CHD7 gene
  - Increased mortality compared to CHARGE without heart defects

Atresia of Choanae (Choanal atresia)

- Present in 30-60%
- No opening for air to pass through the back of the nose because of a membrane of bony tissue
- Causes dramatic breathing difficulties in babies that are nose breathers.
- Requires early operation
- May need re-operations
- Associated with other serious malformations and high mortality

Retarded growth and development

- Often normal length and weight at birth
- Falls off in length in early childhood in spite of normal production of growth hormone in 90% of cases

- Cognition, speech and behaviour:
- Extremely diffucult to assess cognitive level in persons with combined sensory loss
- 50% are said to have IQ>70
- 50% of 4y olds use full sentences in verbal og sign language

Genital anomalies

- Boys:
  - Very often micropenis
  - Retained testicles/cryptorchism
- Girls:
  - Hypoplastic labia

Ear anomalies/deafness

- Very common: In 90-100% one ear will be «typical» CHARGE:
  - Small
  - Low set/outward standing
  - Cup shaped
  - More often anomaly on the same side in case of unilateral nerve palsy (N.facialis).

- Middle ear: Bony defect may contribute to hearing loss

Inner ear, cochlea and semicircular canals

- The semicircular canals are often hypoplastic.
- Causes reduced hearing and problems with balance.
- Present in 90-100%
- Origin of the 8th cranial nerve (N.vestibulocochlearis) (hearing and balance)
  - CT /MRI
  - Findings can rise suspicion of CHARGE/ often CHD7 mutations.

Causes of growth failure

- Main site is the hypothalamus that has connections to the nerve system and endocrine system
- The hypothalamus regulates appetite, sleep, growth, puberty etc.
- The hypothalamus instructs the hypophysis to excrete hormons (GH, FSH, LH)

Hypogonadism

- Both sexes
- Genital hypoplasia, incomplete puberty, infertility
- Early skin puberty (hair, acne, adult body smell)
- Menstruation does not occur (primary amenorea, oligomenorea)

Treatment of hypogonadism

- Boys:
  - Supplementation of testosteron from age 12
  - Follow bone age and testosteron level in blood
  - Better development of secondary sex characteristics, muscles, energy level, self-image
  - Reduces the risk for developing osteoporosis
- Girls:
  - Supplementation of estrogens from age 14 (?), low dose
  - Follow bone age and estrogen level in blood
  - Better development of secondary sex characteristics, self-image
  - Support the prevention of developing osteoporosis

References and sources:

- *https://www.orpha.net/.../Diagnostic_criteria_CHARGE_En_200...*
- *http://tidsskriftet.no/2008/06/oversiktsartikkel/charge-syndromet*
- Dr. Claus Klingenberg, Barneavdelingen, UNN og UiT Norges Arktiske Universitet: Presentation at Frambu 15.02.17.
- Dr. Anne Grethe Myhre, Frambu: Presentation at Frambu 15.02.17.
- Socialstyrelsen.se
- The CHARGE syndrome foundation: https://www.chargesyndrome.org
- Google

Challenging behaviour in rare syndromes

- Behaviour which is not easy to understand, tackle or cope with
- Is there something that the person tries to communicate?
- Learn to read the signs!
  - Physical state
  - Local situation and circumstances
  - Experiences from the person's previous behaviour in similar settings
  - Self stimulation
  - Self mutilation/destructive behaviour
  - Changes of mood
  - Possible pain? (assess pain profile)
- It is easier to change the environment/setting than the behaviour of the person.

What should we focus on?

- The child's well-being, growth and development.
- Symptoms and signs.
- Look for conditions described to be common or rare by the syndrome, like organic manifestations and so on.
- Be aware of preventable failure of development and be prepared to take measures so that it less likely comes true. (ex. scoliosis).
- Think broadly and simply! Syndromic children may get everything that non-syndromic persons also may get!

Important areas of attention and concern

- Nutrition
- Sleep
- Motor function
- Speech and communication
- Social development
- Emotional development
- Mental level and cognition
- Concentration and attention
- Activity (hyper-) and impulsivity
- Behavior and aggression
- Challenging behavior and self mutilation
- Assessment of possible pain conditions

What will need main attention?

- Point out what are the main symptoms and signs of the disorder

- Help patients, service providers and the local health care system to make lists of what they should pay attention to
  - Identify potentially critical medical situations
  - Make plans for how to avoid or prevent these situations
  - Make plans for how to act in case it happens

- Identify preventable failure of development (ex. scoliosis) and risk for comorbidity

The caring and supportive system

- Health station, community level
- The assigned local doctor («fastlege»)
- Kindergarden, school, «PPT»
- The responsibility group
- The respite home
- The specialized health services: Specialist clinics, departments, Habilitation units for children and adults (Barnehab. and Voksenhab), Psychiatry units for children and adults (BUP, Voksenpsykiatrien)
- Frambu komptansesenter for sjeldne diagnoser, TAKO, Signo, Statsped, m.fl.

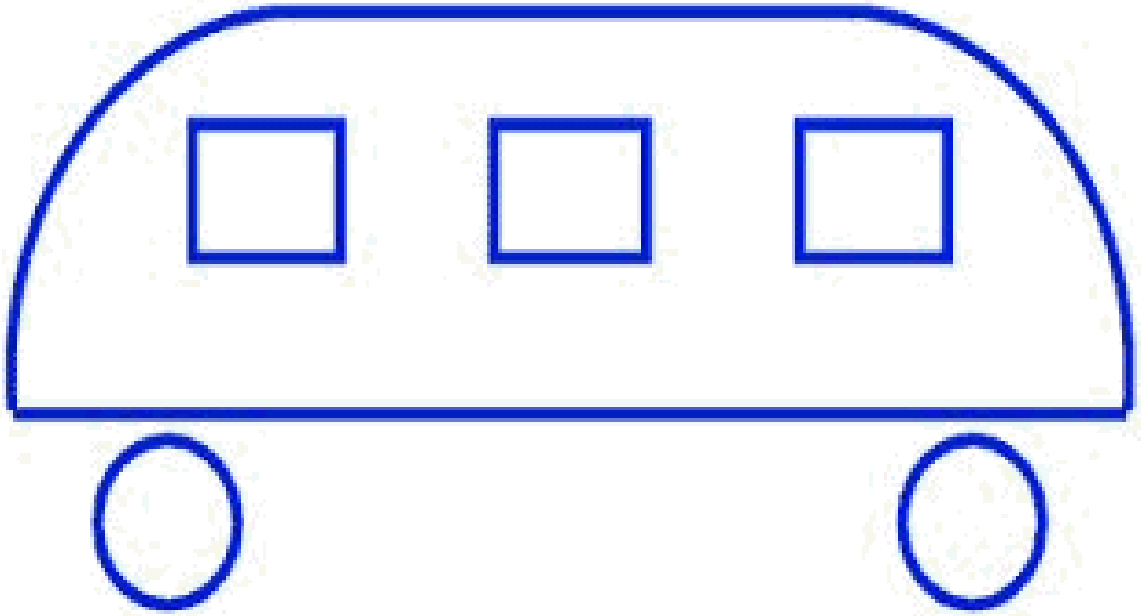
Important elements in the follow-up of persons with one of the diagnoses of Frambu, like CHARGE:

- A functioning ”responsibility-group” around the child/person and his family
- An interested general practitioner/local doctor
- A stimulating kindergarden and school
- An including (and may be sheltered) working place in time coming
- Communication which is understandable both ways
- Provide for getting overview and control through day plans and good structure
- Engaging and involving activities in leisure time
- Bodily exercise that takes care of physical and mental well-being
- Environment that protects and makes you feel safe
- Understanding caregivers, loving communities and accepting societies

To sum up:
Visions and goals for Frambu:

- To be a meeting place and a learning place for users, their families, care givers and support service system.
- To give reliable and correct information and share experiences about the diagnosis and its challenges.
- Contribute to a more hollistic and equal follow-up for persons with a Frambu-diagnosis all over the country, through dialogueing with professionals in the interdisciplinary support service.
- Instead of contributing to resignation and despair: Learn to live with!
- Empowerment: Support and strengthen the users and their families in meeting and tackling the challenges of daily life in a better and more appropriate and confident way!

So, where is the bus heading for now??!



Thank you!

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