Syndromology

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Syndrome

- A combination of several anomalies and malformations, which occurs repeatedly together and creates a characteristic clinical picture – **phenotype**
- No symptom is pathognomonic and none is mandatory for a particular syndrome (but some databases show a percentage for a particular syndrome).
- Their occurrence is decided at the time of conception (for phenocopies in early embryonic development)
- They do not manifest themselves in the whole spectrum of symptoms at the time of child birth or early infancy
- The diagnosis is usually not made during the 1st genetic examination, the child must be monitored and cooperated with other medical disciplines → **multidisciplinary approach**

Syndrome

- The importance of family photography, the symptoms may increase or decrease with age
- Syndromological diagnostics places high demands on time, own and literary experience, there are a large number of affections, their population incidence is low, we do not have to see them in our entire professional life
- The importance of international cooperation for the diagnosis of rare diseases
- The importance of a general practitioner for children and adolescents and a pediatrician or outpatient specialist - they have data from the birth of a child, they know the family and can speed up the diagnosis
- Clinical genetics - evaluates the prognosis, can suggest therapeutic and **preventive measures**, clarifies the genetic causes of the child's disability, makes it easier for parents to accept the diagnosis

Syndrome

- **Different population frequencies**
- Klinefelter's syndrome 1: 500
- Turner syndrome 1: 2,500
- Marfan's syndrome 1:10,000
- Alagille syndrome 1:30,000
- Xeroderma pigmentosum 1: 2 mil.

Concepts

- Small dysmorphic anomalies
- Signal symptoms
- Genetic heterogeneity
- Phenocopy
- Molecular heterogeneity

Small dysmorphic anomalies

- They are not rare, we observe them at 10 -15% of the population
- They occur in isolation
- The are clinically insignificant
- Usually they are external symptoms - the importance of examination by sight
- E.g. protruding ears, disproportion of the length of the fingers, toes, aberrant patterns of flexion palm and finger lines, less common inclination of the eye slits, etc.

Small dysmorphic anomalies

- If a child has *2-3* such symptoms, they may be a signal of the presence of one or more malformations of various organ systems as a manifestation of a severe morphogenesis disorder in ontogenesis.

- Even normally occurring signs can become anomalies if they persist or manifest at an unusual stage of development, e.g. open large fontanelle in a child over 18 months of age, small stature, disproportionately large head, etc.

- Small anomalies are a valuable differential diagnostic guide and are referred to as **signaling symptoms**

Genetic heterogeneity

- The same syndrome can be inherited in an autosomal dominant or recessive inherited form

- Different genes affect the same pathogenetic pathway

Phenocopy

- Teratogenic embryopathy can mimic the genetic syndrome, i.e. Maternal PKU syndrome

- high concentration of phenylalanine in the mother's blood causes microcephaly, congenital heart disease and mental retardation in the offspring

Molecular heterogeneity

- Different point mutations in one gene, gene microdeletion, uniparental disomy, mosaic - their consequences can be significantly different for the genetic prognosis of reproduction in the family

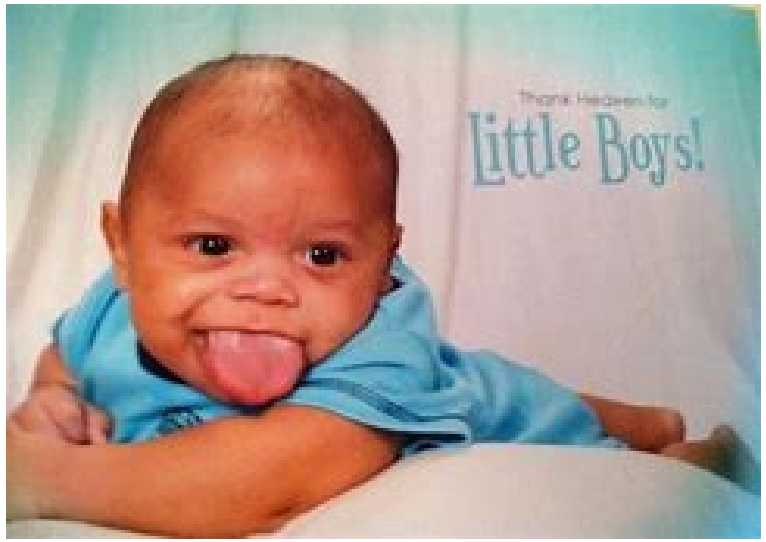
An overview of examples of somatoscopically detectable small anomalies and symptoms

- They most often focus on the face, ears, hands, feet and genitalia (boys)

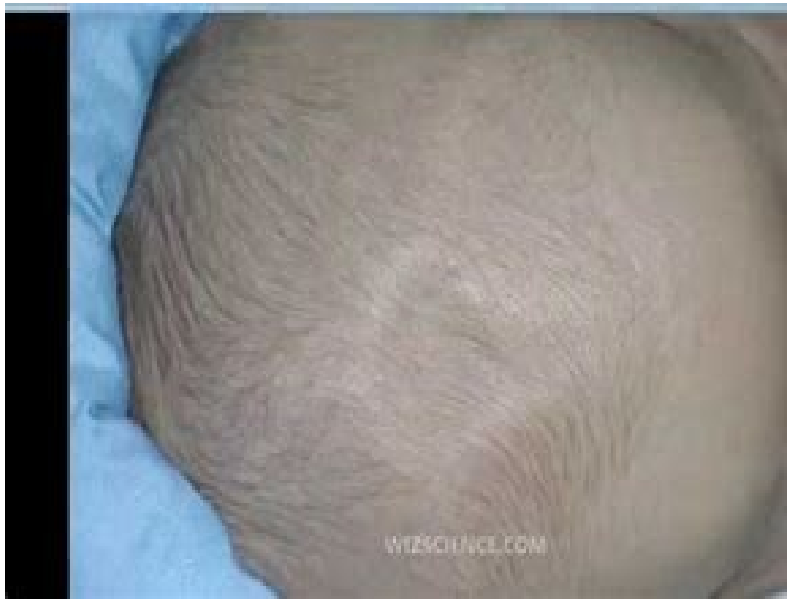
- Often combined with growth retardation and retardation of psychomotor development

Lower birth weight to gestational age, small for gestational age, intrauterine growth retardation

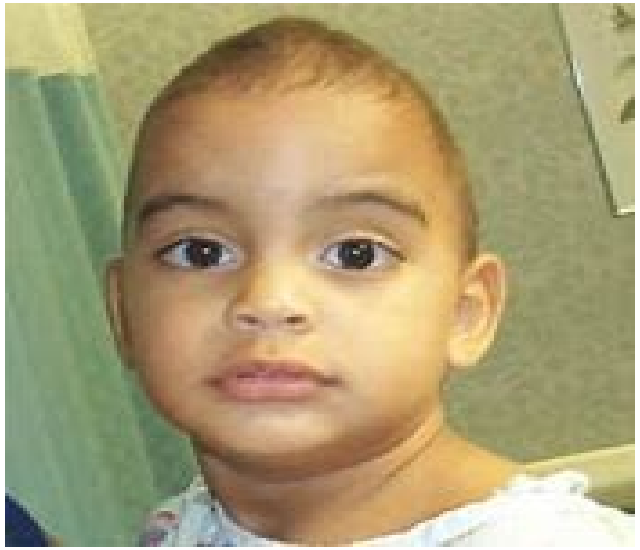
Higher birth weight to gestational age, huge newborns



Large fontanelle-late closure after 18 months of age, irregular large fontanelle, wide open large fontanelle



Large fontanelle - premature closure, premature adhesion of e.g. sagittal suture, importance of measuring frontooccipital circumference



Severe muscle hypotonia, floppy baby

Atypical distribution of fat on the body

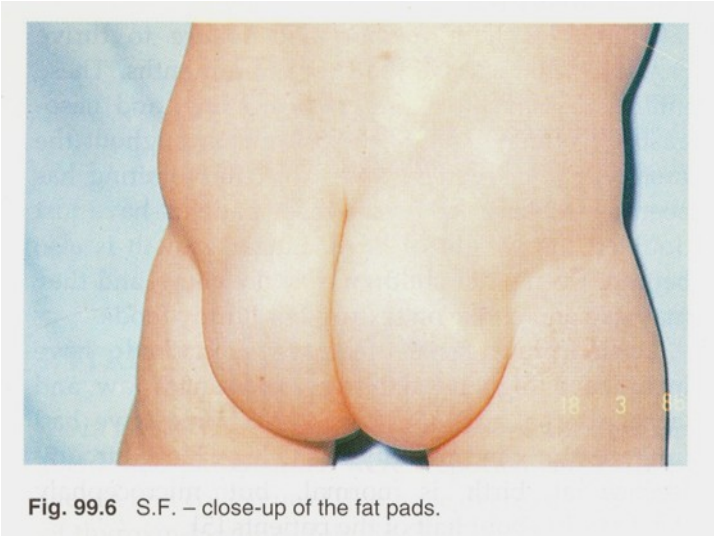


Fig. 99.6 S.F. – close-up of the fat pads.

Delayed growth, small growth <3rd percentil for a given age

Accelerated growth, high growth> 97th percentil for a given age

Overweight (BMI 90th - 97th percentil) and obesity (BMI> 97th percentil)

Facial dysmorphia

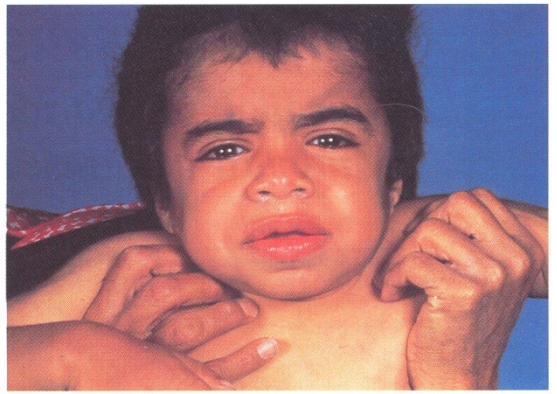
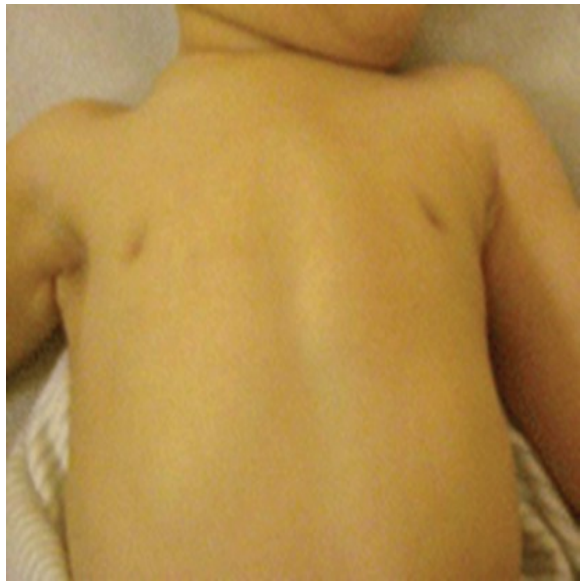


Fig. 74.3 A.D.F.S., an 8-year-old boy with Hunter disease. The facial features were quite coarse, the hairline low and the eyebrows abundant, and the lips were very full. Iduronate sulfatase activity was absent.

Iris heterochromia

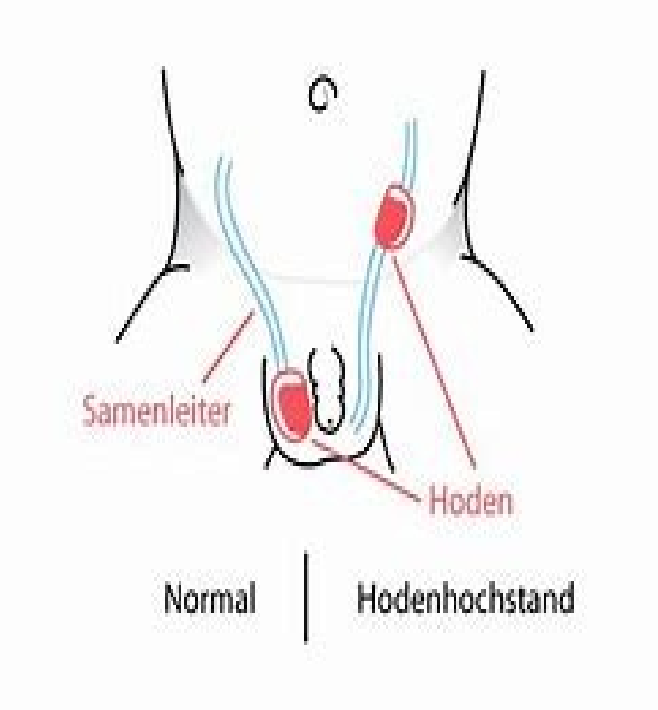
Bulbous nasal tip

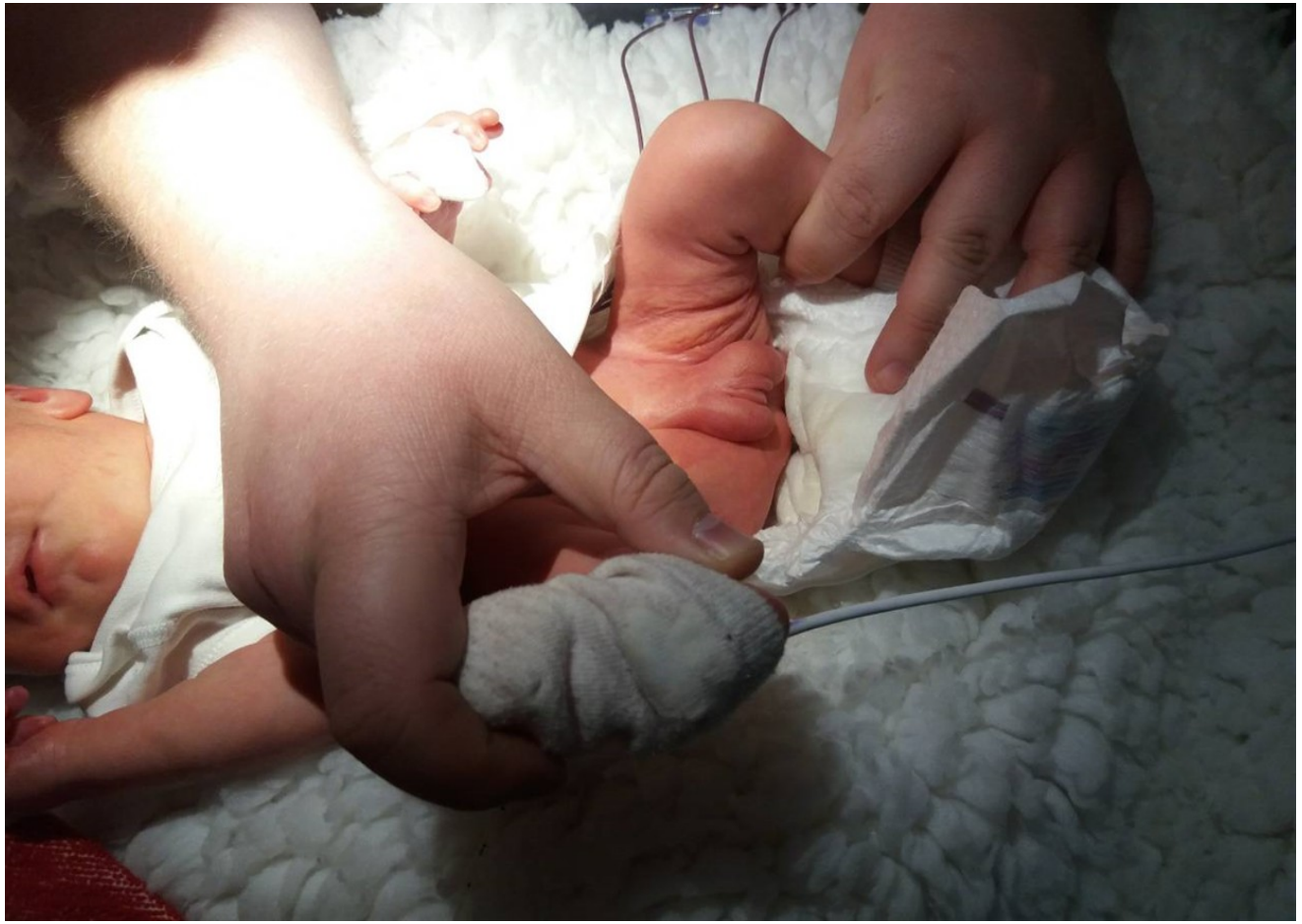
Atypical nipples - inverted



Dysplastic lobes, lower set, rotated and small or large, small chin

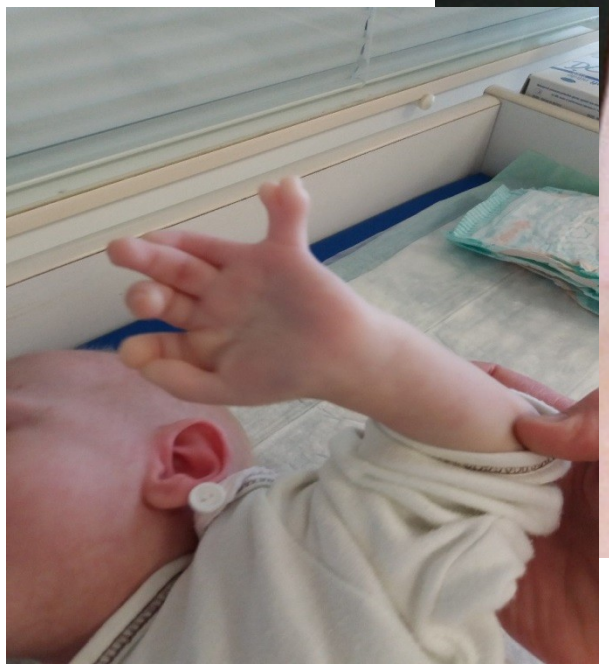
Hypogenitalism, hypogonadism, cryptorchidism, ambiguous genitalia

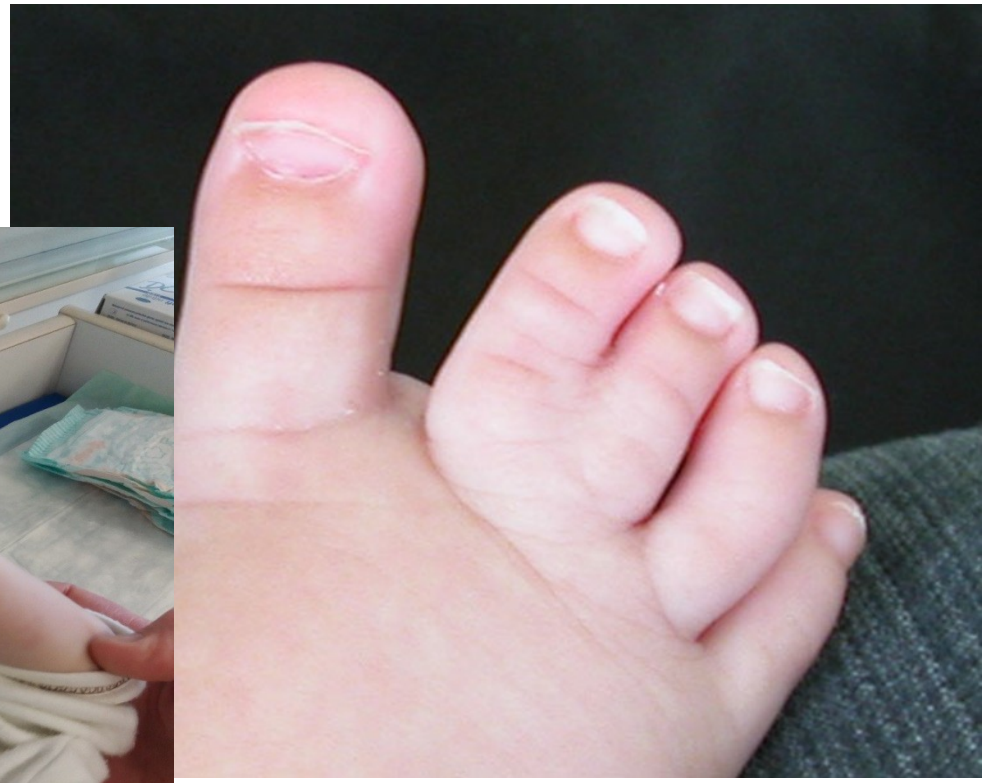




Cutis laxa, loose skin

Arachnodactyly, brachydactyly, syndactyly, polydactyly, wide thumbs





Microdeletion syndrome

- I.E. Alagille syndrome (ALGS), Prader-Willi syndrome (PWS), Williams-Beueren syndrome, etc.
- Typical facies
- Typical occurrence of congenital heart disease
- There may be mental disabilities of varying degrees
- They usually arise as "de novo" mutations, but also as inherited mutations
- Case report of a child with ALGS

Subtelomeric rearrangement

- Cause about 7% of mental retardations
- Phenotype: facial dysmorphia, dysplastic ears, dermatoglyph anomalies, microcephaly, growth and development retardation
- Examination is indicated for dysmorphic features and unexplained developmental disorders

Mosaic affections (approx. 1% of the population)

- I.E. Sturge-Weber syndrome, SWS
- Early postzygotic chromosomal or gene mutations lead to the development of two or more cell lines with different genetic equipment
- There is the development of poor placental function or the development of malformations and anomalies
- Presence of affection only in a part of cells - affection has a clinically less severe course compared to the full form, when the affection can be up to lethal

Syndromes of chromosomal instability, immunodeficiency and hypersensitivity to mutagens

- I.E. NIJMEGEN BREAKAGE SYNDROME; NBS, ataxia telangiectasia variant V1
- Enzymatic disorders at the DNA level leading to DNA repair failure
- It most often affects rapidly dividing cells
- High risk of malignancies

Syndromes caused by a trinucleotide repeat expantion

- I.E. Fragile X syndrome, FXS;
- Caused by a trinucleotide repeat expantion
- They depend on the sex of the parent from whom the child inherits the mutation
- Presence of **premutation** in the parent - the presence of an increase in the number of trinucleotide repeats from normal to abnormal numbers

- I recommend you look at all the syndromes listed here on the Internet or in a textbook

- Case reports (PKU, ALGS, HPP)