Dysmorphology

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Dysmorphic presentation

- Congenital malformation
  - Disorder of embryogenesis
    - Intrauterine insult – infection; chromosomal/genetic or metabolic
- Postnatal
  - Normal at birth but later remodelling
    - Accumulation of toxic metabolites

Congenital dysmorphology – disorders of embryogenesis

- Disorder due to maternal IEM
  - Maternal PKU
- Disorders due to fetal IEM
  - Peroxisomal disorders
  - Disorders sterol metabolism
  - Disorders of energy metabolism
  - Congenital disorders of glycosylation
  - Others

Postnatal dysmorphology - remodelling

- Lysosomal disorders, especially MPS
- Amino acid disorders
- Trace metal disorders
- Many others

Disorder of embryogenesis – Maternal PKU

- 90% infants born to mothers with phe >1200umol/L have congenital abnormalities
- Metabolic teratogenesis resembling fetal alcohol syndrome
- Microcephaly, IUGR and facial dysmorphism, severe learning difficulties, congenital heart disease and other malformations
- Has mother been screened for PKU?

Disorders of the fetus
Peroxisomal disorders

- Peroxisome biogenesis disorders
  - Zellweger/NALD/IRD
- Rhizomelic chondrodysplasia punctata
  - Single or multiple enzyme defects
- Single peroxisomal beta-oxidation defects
  - Especially bifunctional protein defect

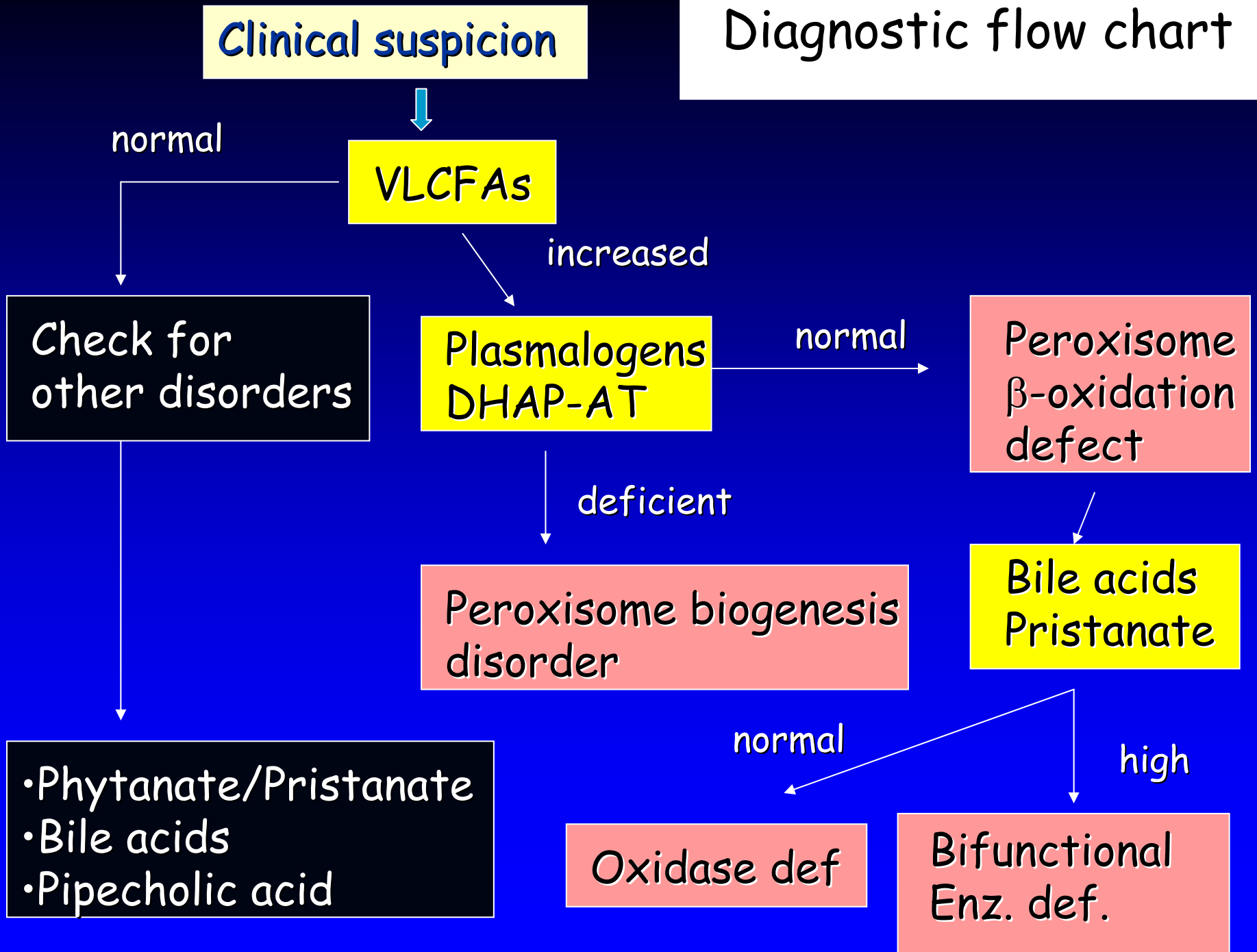
Peroxisomal biogenesis disorder -Zellweger syndrome

- Typical facial dysmorphism: high forehead, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthic folds
- Profound hypotonia and seizures
- Retinopathy, cataracts, hearing loss
- Enlarged liver
- Renal cysts
- Punctate stippling esp. patella and epiphyses

Biogenesis and beta-oxidation disorders biochemical tests

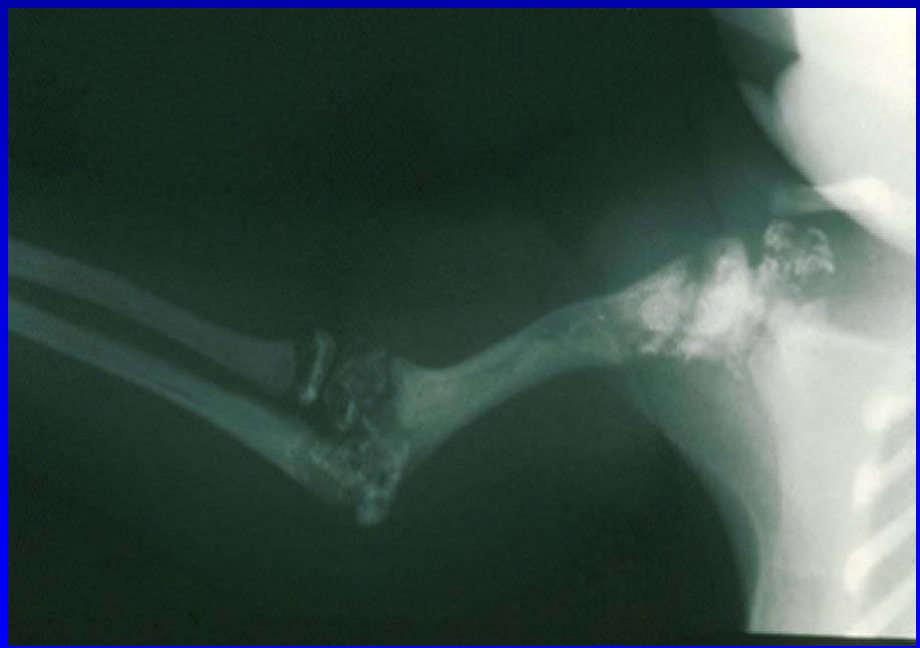
- Plasma VLCFA
  - Plasma phytanate/pristanate
  - Plasma bile acid intermediates
  - Red cell plasmalogens
  - Platelet/fibroblast DHAP-AT assay

Diagnostic flow chart

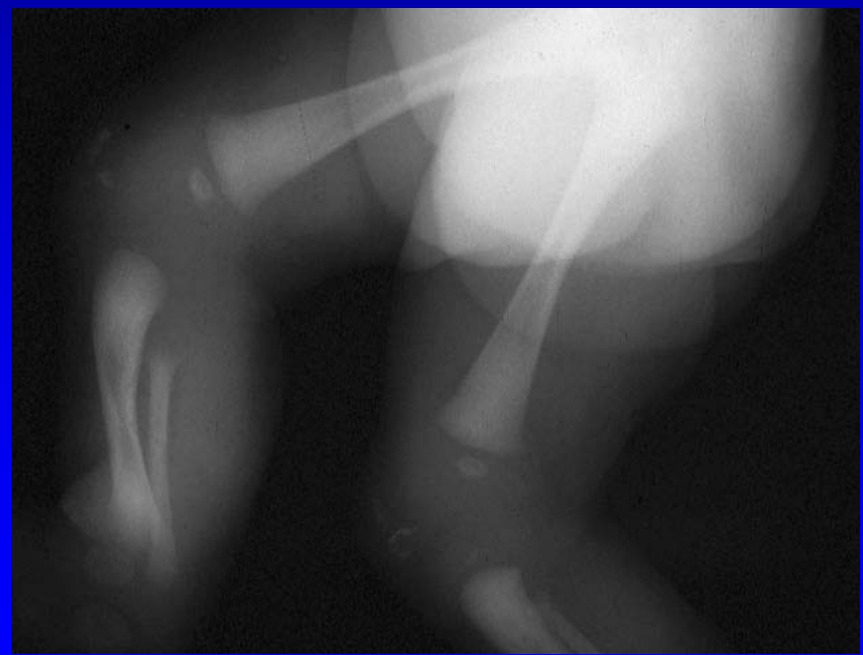


Calcified (punctate) stippling and rhizomelia

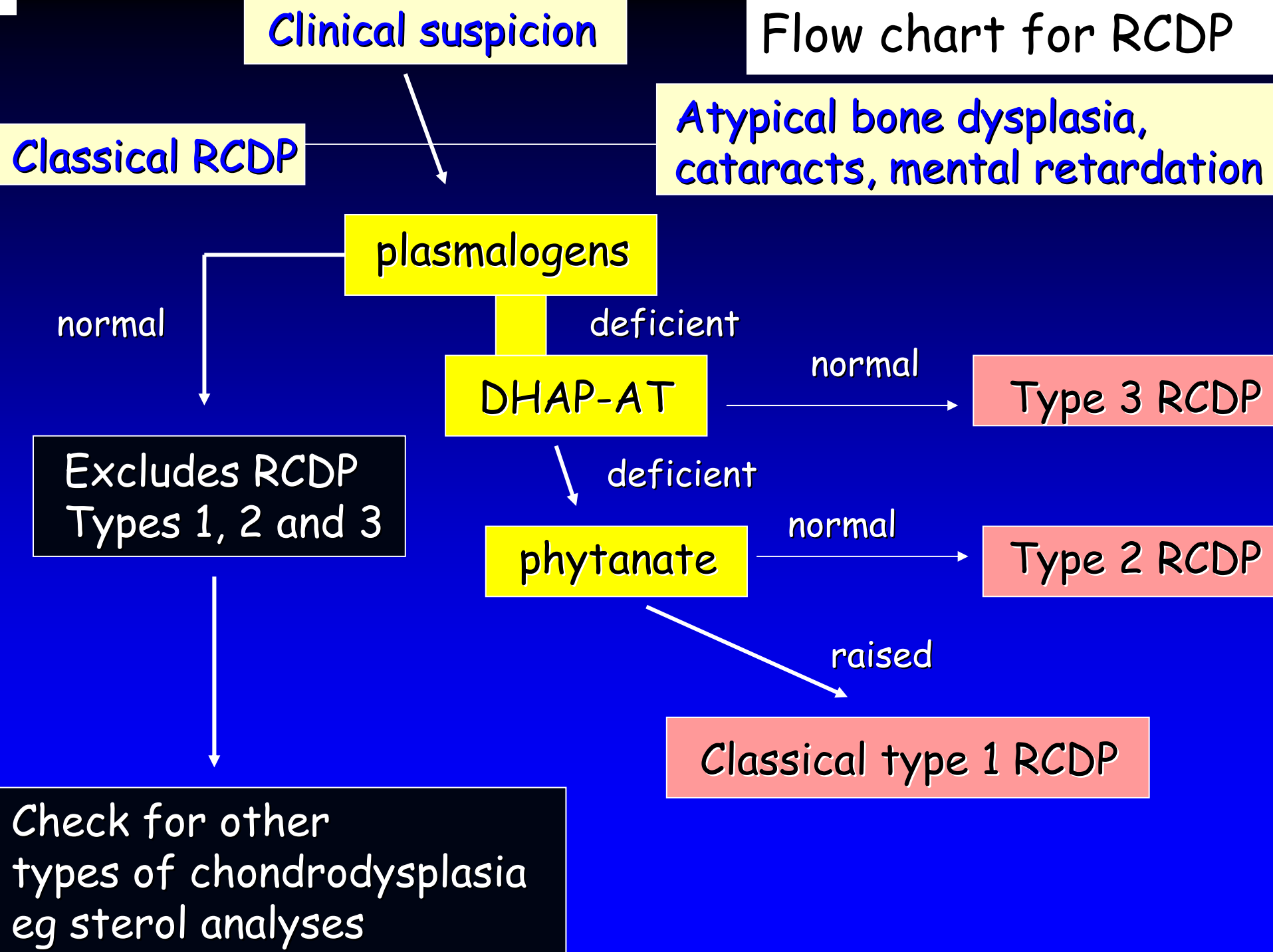
RCDP



Zellweger

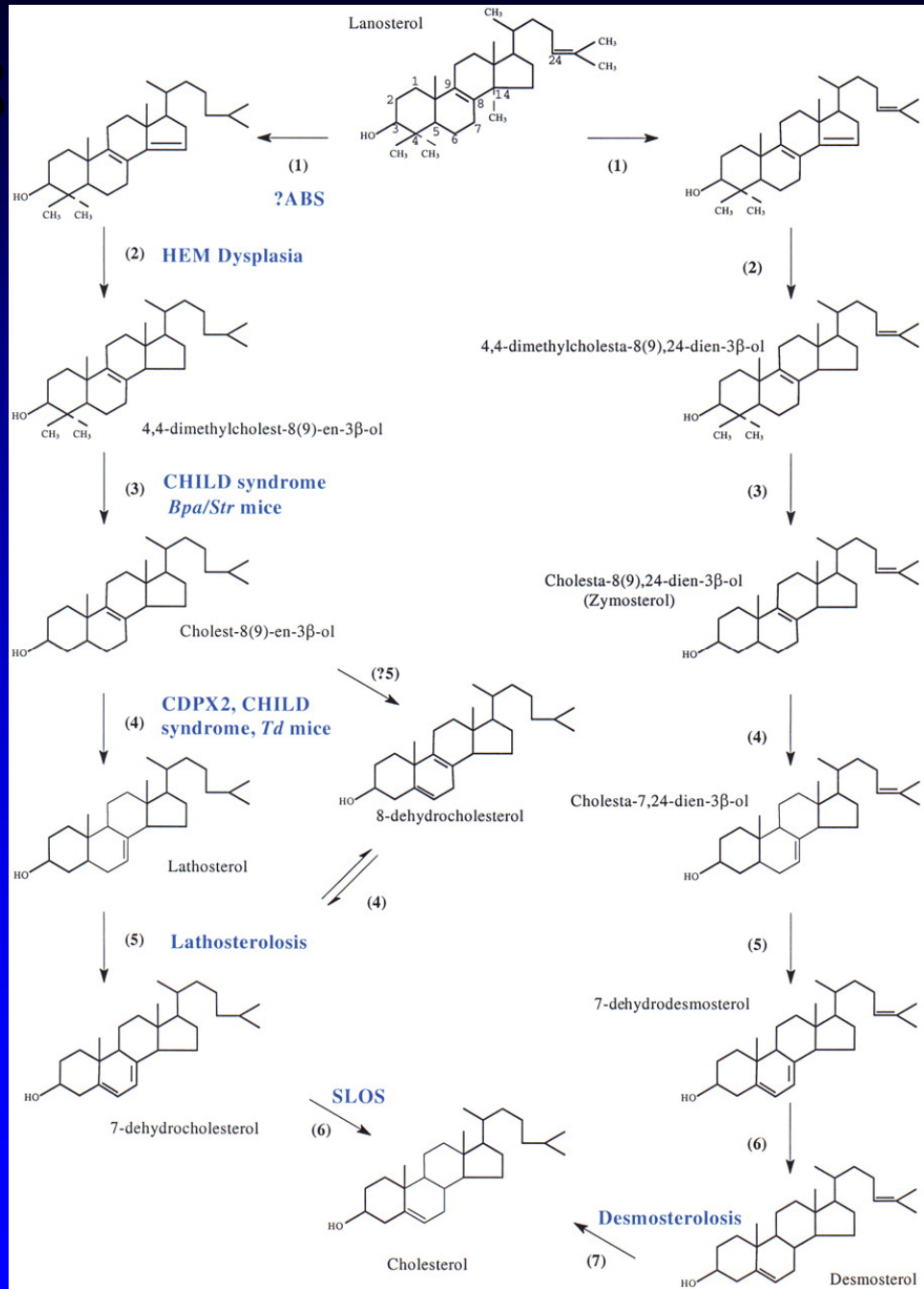


Flow chart for RCDP



Sterol disorders

- Mevalonic aciduria
- Smith-Lemli-Opitz syndrome
- Desmosterolosis
- Lathosterolosis
- Conradi-Hunermann syndrome
- CHILD syndrome



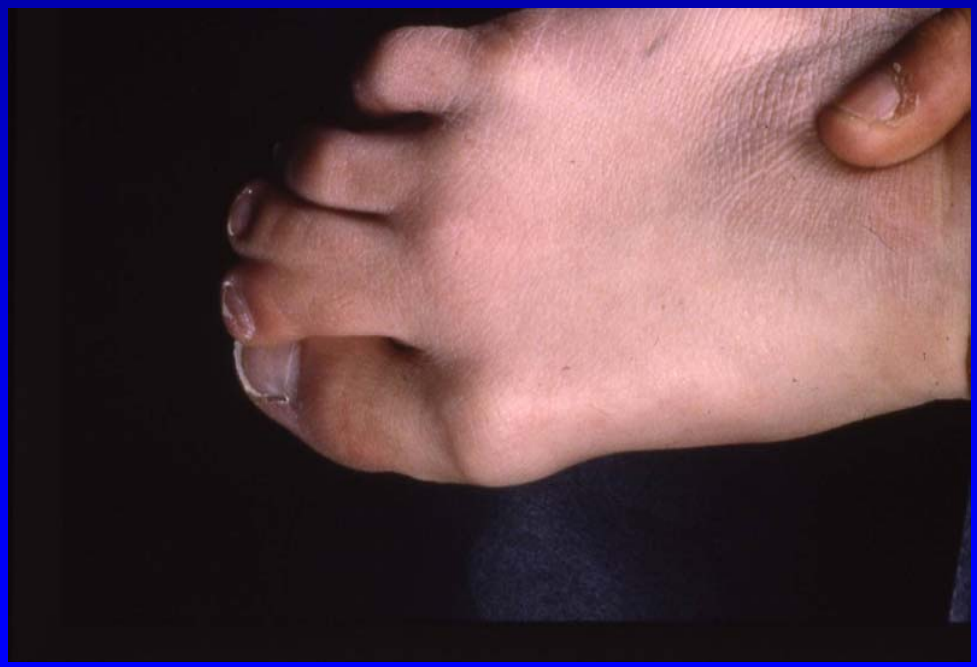
Mevalonic aciduria - mevalonate kinase deficiency

- Psychomotor retardation, failure to thrive, and hypotonia are common
- Severely affected patients have microcephaly, short stature dolichocephaly, wide fontanele, low set ears, blue sclerae and cataracts. Cerebellar hypoplasia.
- Febrile crises, hepatosplenomegaly, lymph-adenopathy, diarrhoea and rashes may be present
- Diagnosis by urine organic acids – increased mevalonic acid and lactone

Smith-Lemli-Opitz

7-dehydrocholesterol → cholesterol

7-DHC reductase deficiency



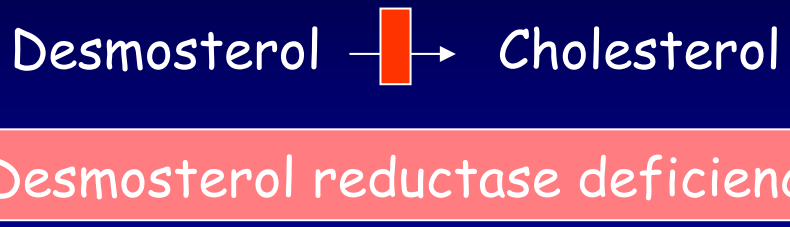
Smith-Lemli-Opitz syndrome

- Severe type II presentation
  - Stillborn or neonatal presentation with major malformations: polydactyly, cleft palate, structural abnormalities in brain, heart and kidneys
- Type I presentation
  - craniocial (microcephaly, ptosis, anteverted nares, retrognathea etc),
  - skeletal (syndactyly),
  - genital (hypospadias, cryptorchidism),
  - develpoment (growth and mental retardation, feeding problems)

SLO diagnosis

- Diagnosis by sterol analysis of plasma or tissues
- GC-MS analysis of 7-DHC and isomer (8-DHC) usually reliable although levels in milder patients may only be slightly high
- Free cholesterol is usually reduced in plasma but routine analyses are usually unreliable since dehydrocholesterols also react in the oxidase assay

Desmosterolosis



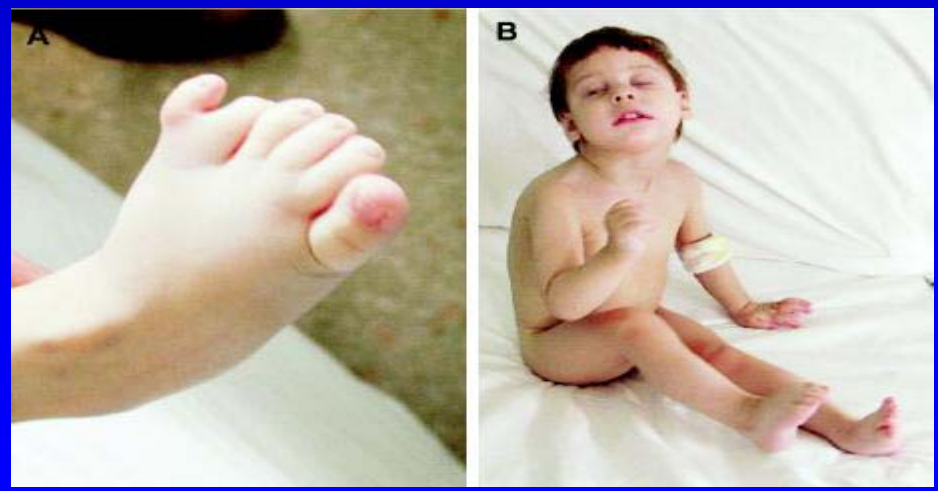
- Few cases reported, first case in fetus with multiple malformations (growth deficient, rhizomelic limb shortening, facial dysmorphism, ambiguous genitalia etc)
- Two subsequent cases milder with severe dev delay, cleft palate, small mandible)
- Diagnosis as for SLO but looking for desmosterol – plasma sterols

Lathosterolosis

Lathosterol → 7-dehydrocholesterol

Lathosterol 5-desaturase deficiency

- Mental retardation, polydactyly, vertebral abnormalities, liver disease
- Plasma sterols show high lathosterol



Conradi-Hünermann syndrome

Sterol-Δ8-isomerase deficiency

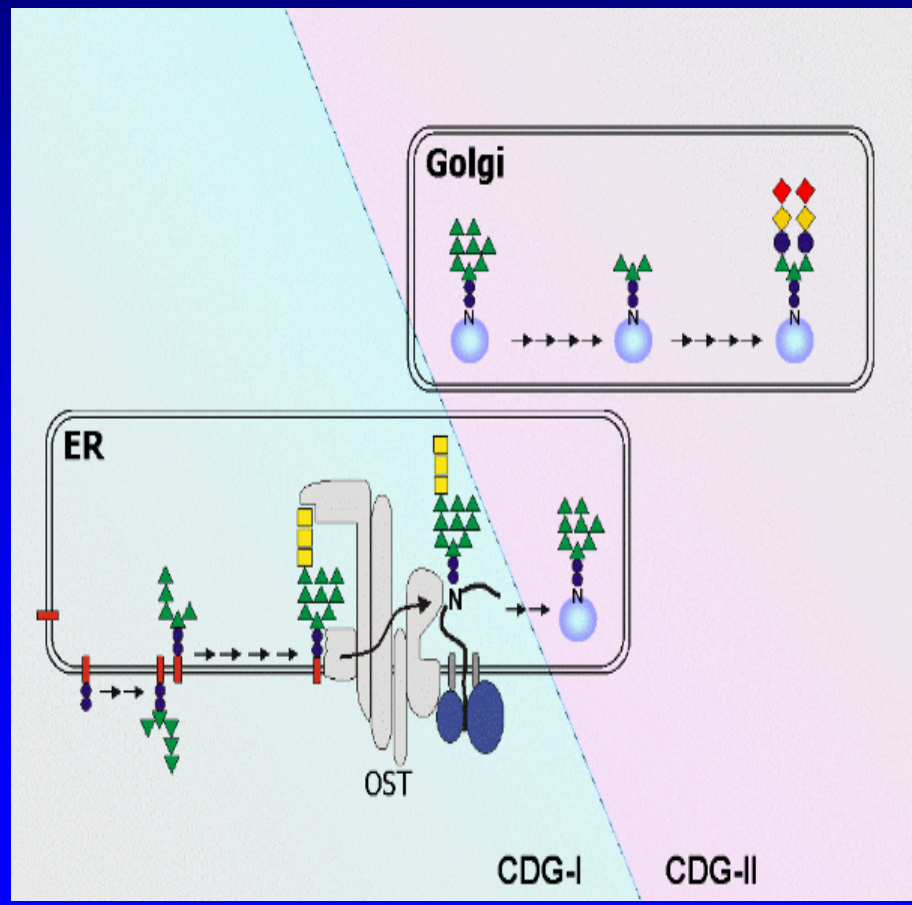
- X-linked dominant
- Ichthyosis, cataracts, short stature, punctate calcifications and asymmetric limb shortening
- Maybe similar to CHILD syndrome (congenital hemidysplasia, ichthyosis and limb defects)
- Plasma sterol analysis

Disorders of energy metabolism

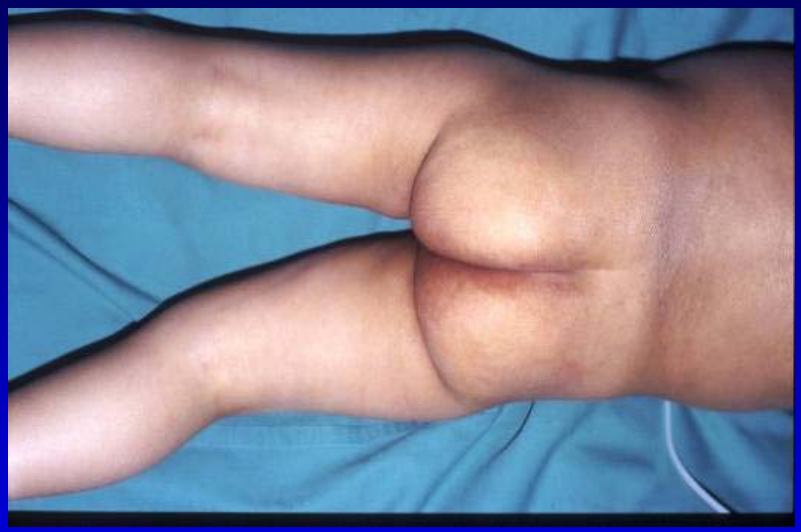
- Pyruvate dehydrogenase deficiency
  - Cerebral malformations, agenesis of corpus callosum, facial dysmorphism, metabolic acidosis
  - Blood and CSF lactate, fibroblast PDH assay and mutations
- Mitochondrial respiratory chain defect
  - Muscle respiratory chain assays, mutation analyses
- GAII
  - Dysmorphic, renal cysts, characteristic smell
  - Defective ETF or ETF-DH
  - Test organic acids and acylcarnitines

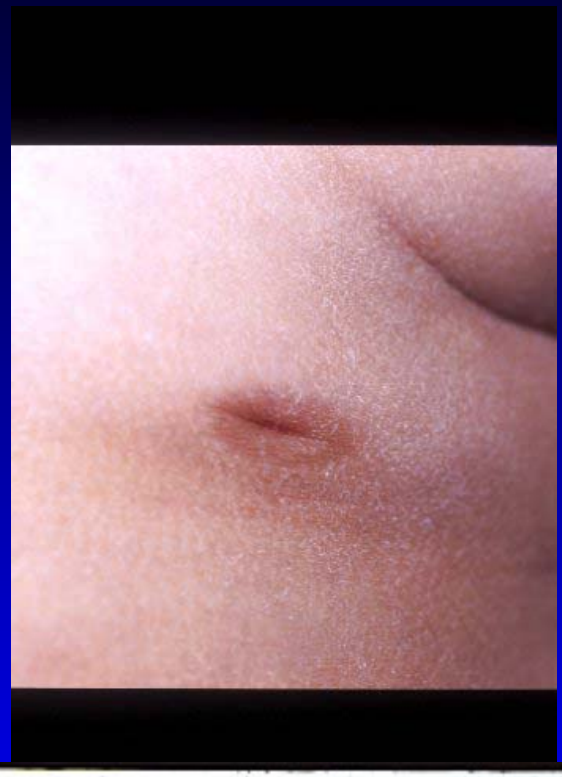
Congenital disorders of glycosylation - CDG syndromes

- Protein glycosylation is either through asparagine (N) or serine/threonine (O)
- There are some 18 different disorders of glycosylation
  - CDGI are N-linked (12)
  - CDGII are O-linked (6)
- Diagnosis by transferrin isoelectric focussing

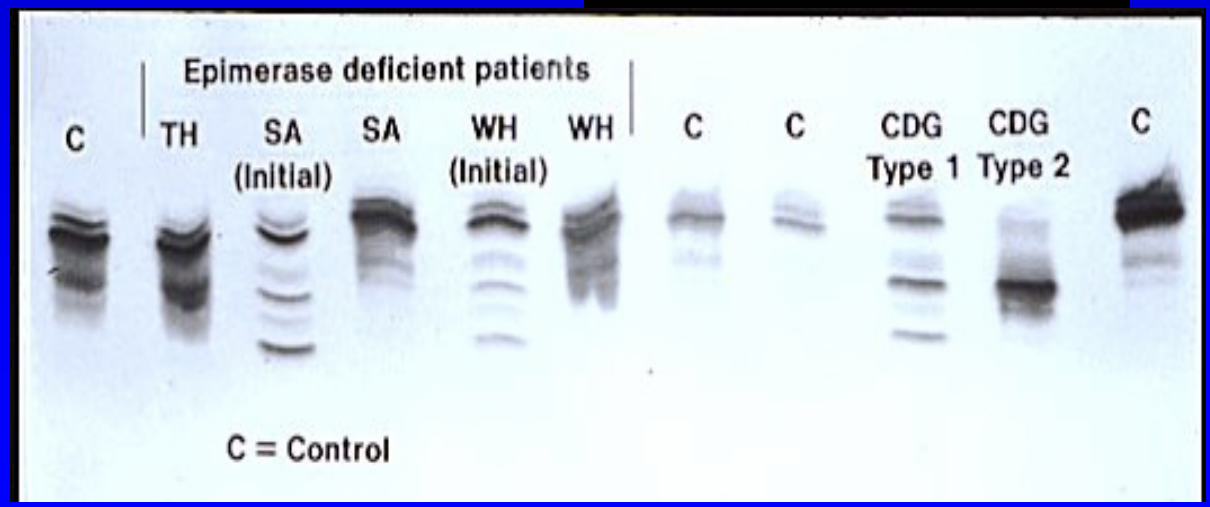


CDG syndrome





Transferrin isoelectric focussing



Molybdenum cofactor/Sulphite oxidase deficiency

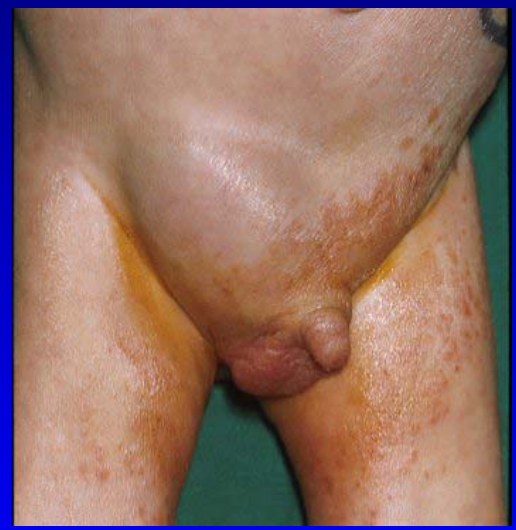
- Diagnosis
  - Low uric acid
  - Positive urine sulphite test
  - Increased sulphocysteine in urine and plasma, low plasma cystine

Postnatal dysmorphic disorders

- Remodelling of bone and soft tissue
  - lysosomal storage disorders
    - MPSI - MPS VII
    - Mucolipidosis II
    - GM1-gangliosidosis
    - alpha mannosidosis
    - galactosialidosis
    - multiple sulphatase deficiency
- Connective tissue effects
  - Homocystinuria
  - Menkes disease

Lysosomal storage disorders

- Usually presents in the first months
- But may present with fetal hydrops
  - Especially MPSVII
- Or as colloiden baby (Gaucher disease)

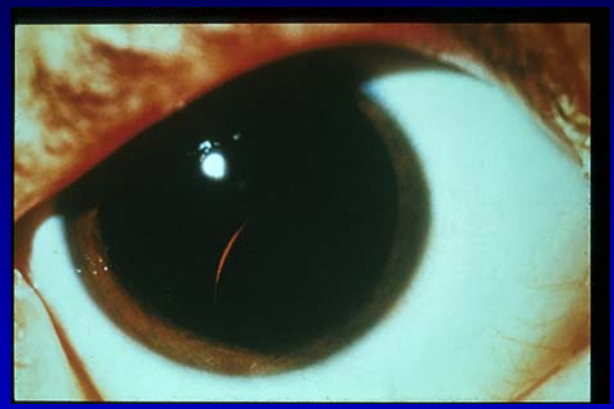


Lysosomal disorders - diagnostic tests

- MPS disorders:
  - Urinary MPS analysis
  - Specific enzyme assays
- Other lysosomal disorders:
  - Specific enzyme assays
  - Sialic acid analysis

Urinary MPS electrophoresis

Homocystinuria



- Marfanoid features
  - Skeletal abnormalities
  - Osteoporosis
  - Dislocated lenses
  - Mental retardation, thrombosis, seizures
- Diagnosis
  - Increased homocystine in plasma and urine, increased plasma methionine

Menkes

- X-linked disorder of copper transport
- Low plasma Cu^{++} and ceruloplasmin
- Fibroblast copper uptake studies/DNA

Metabolic disease and Dysmorphology

- Maternal PKU
- Peroxisomal disorders
- Disorders of sterol metabolism
- Disorders of energy metabolism – PDH
- Congenital disorders of glycosylation
- Molybdenum cofactor/Menkes disease
- Lysosomal disorders