# Smith-Lemli-Opitz syndrome from an international perspective

PD Dr. Dorothea Haas

# A mysterious patient - how it all started…

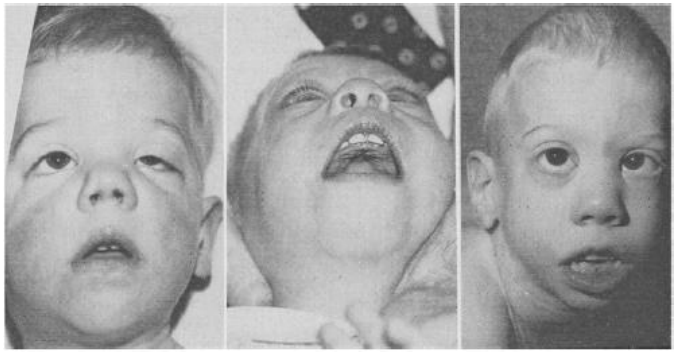
- 1 year old girl
- Feeding difficulties
- Slight developmental delay
- Muscular hypotonia trunc
- Muscular hypertonia extremities
- Small head and peculiar face
- Deformed feet
- Syndactyly toes 2 + 3

# Some explanations

- syndrome: symptoms not correlated with each other but associated with a specific disorder
- dysmorphic feature, dysmorphism: difference of body structure

# Smith-Lemli-Opitz syndrome

- First described in 1964
- 3 boys with
  - Developmental delay
  - Feeding difficulties
  - Failure to thrive
  - Specific dysmorphic features

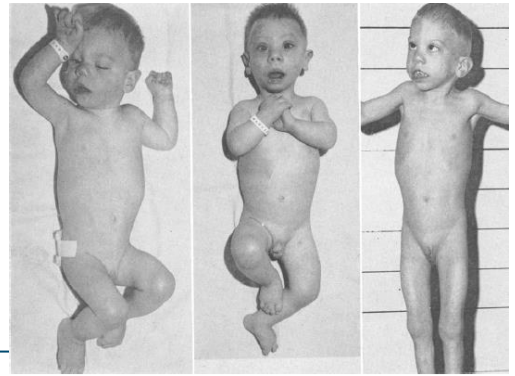


*A newly recognized syndrome of multiple congenital anomalies*

*Three unrelated male children have been found to have a strikingly similar pattern of multiple congenital anomalies which suggests a common etiology. In addition to relative microcephaly with mental retardation and hypertonicity, these patients have incomplete development of the external genitals and abnormalities of the face, hands, and feet. Congenital pyloric stenosis was present in two of them. No chromosomal abnormality was found and the cause remains obscure though the apparent occurrence of the same condition in a deceased sibling of one of the patients suggests a genetic determination.*

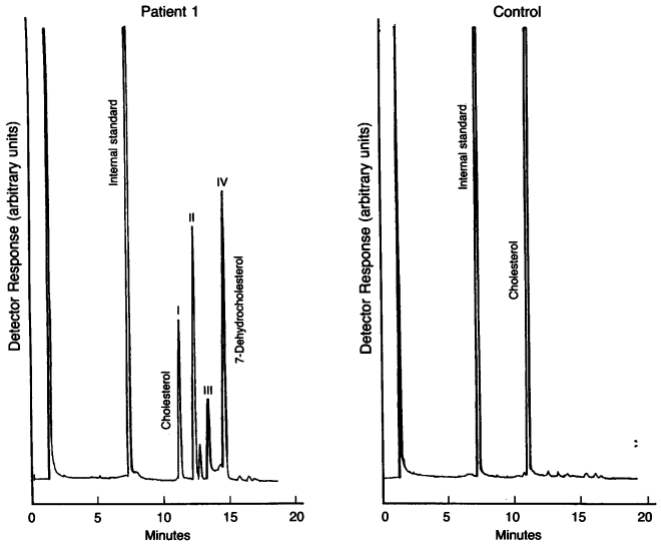
David W. Smith, M.D.,* Luc Lemli, M.D., and John M. Opitz, M.D.

MADISON, WIS.



# Biochemical abnormalities in SLOS

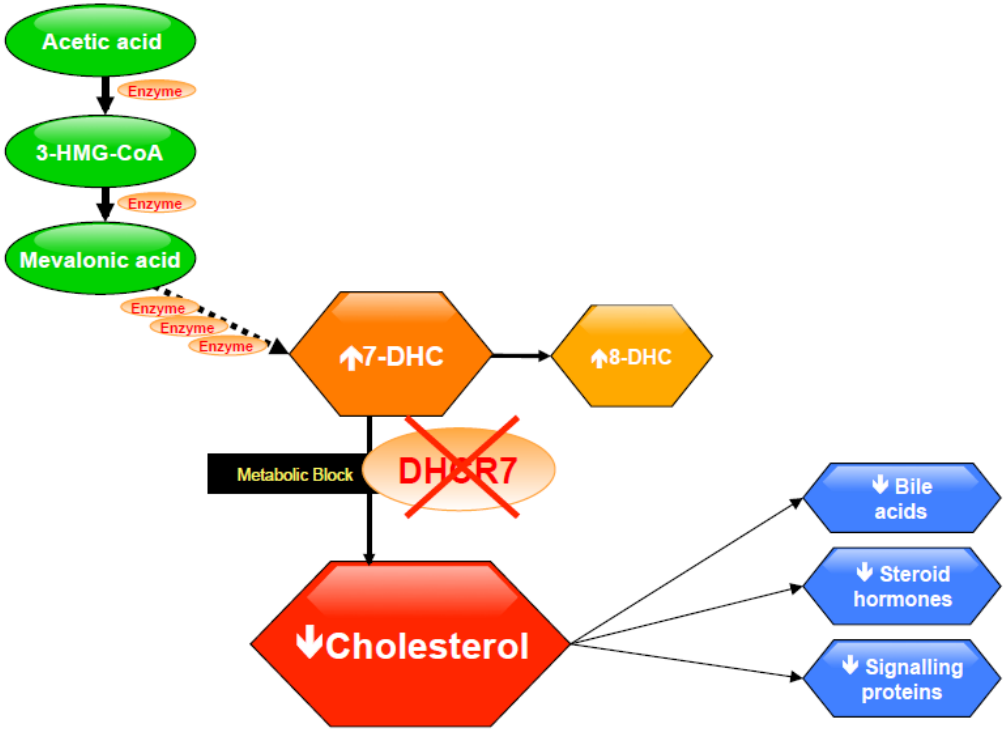
- 1993/1994 M. Irons / S. Tint
- Biochemical abnormalities in blood of 5 patients with SLOS:
  - Low concentration of cholesterol
  - Elevated concentration of 7-dehydrocholesterol




Irons et al., Lancet 1993

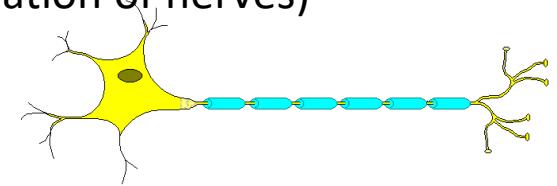
Tint et al., NEJM 1994

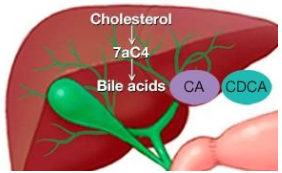
# SLOS is caused by a defect of cholesterol synthesis



# Cholesterol functions

- Structural element of membranes and myelin (insulation of nerves)
- Important component of
  - Caveolae and lipid rafts (intracellular transfer)
- Precursor for the synthesis of
  - Bile acids
  - Steroid hormones
  - Neurosteroids
  - Embryonic signalling proteins
- Biosynthesis pathway important for
  - Glycosylation
  - Translation of proteins
  - Differentiation of cells
  - Mitochondrial electron transfer

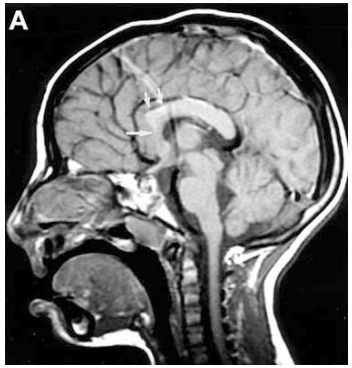




# SLOS – malformations due to intrauterine cholesterol deficiency

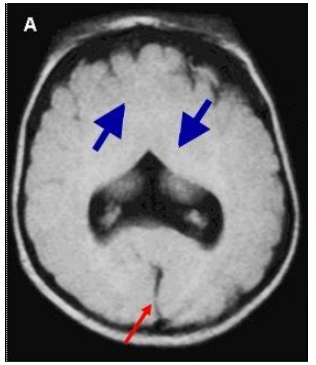
- Brain: midline defects (37 %)
- Cleft palate (47 %)
- Heart: ASD, VSD (54 %)
- Kidney: hypoplasia, ectopia, cysts, malformation of urinary tract (43 %)
- Genital: hypospadia, undescended testicles (65 %)
- Skeletal: foot deformity, redundant fingers or toes (48 %), syndactyly 2/3 (95 %)

Kelley, Hennekam J Med Genet 2000




Caruso et al. Neuroradiology 2004

Haas, Mohnike, Robbin (Hrsg) Mabuse-Verlag 2013

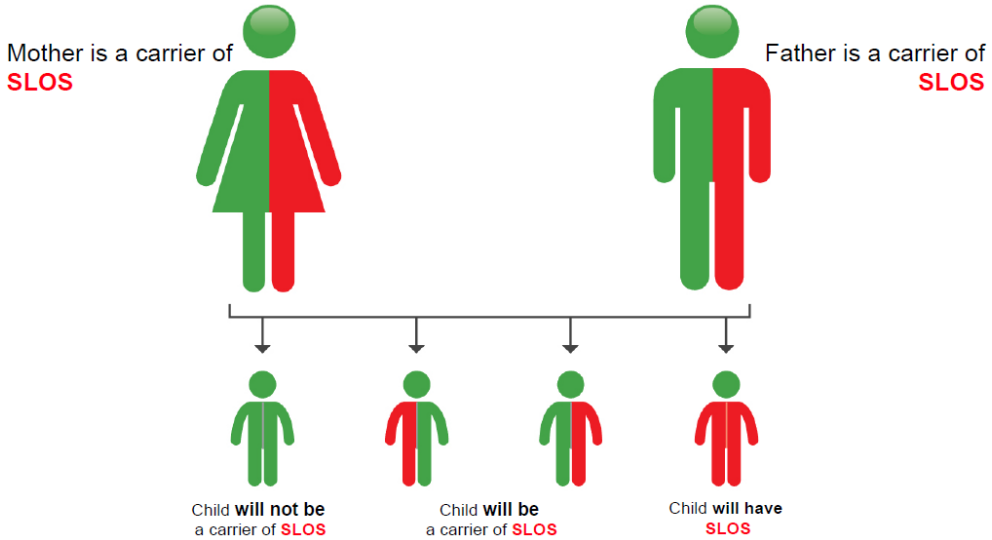



Solomon et al. GeneReviews 2000

# Genetics

## Inheritance

**Autosomal-recessive - possible combinations**




Supported by NUTRICIA as a service to metabolic medicine

Written by Haas & Burgard 16

# Frequency and distribution of SLOS

- Incidence 1:10.000 to 1:60.000 newborns in Europe
- Most frequent in Eastern Europe (Czech Republic)
- Less frequent in Asian and African populations
- Sweden: 10 mio. inhabitants, 166 SLOS patients

# SLOS - Variability of presentation

**Severe phenotype**

- Malformation of internal organs
- Persistent  severe feeding difficulties
- High risk for severe infections
- Severe psychomotor+ cognitive impairment
- Behavioual problems are not prominent

**Moderate phenotype**

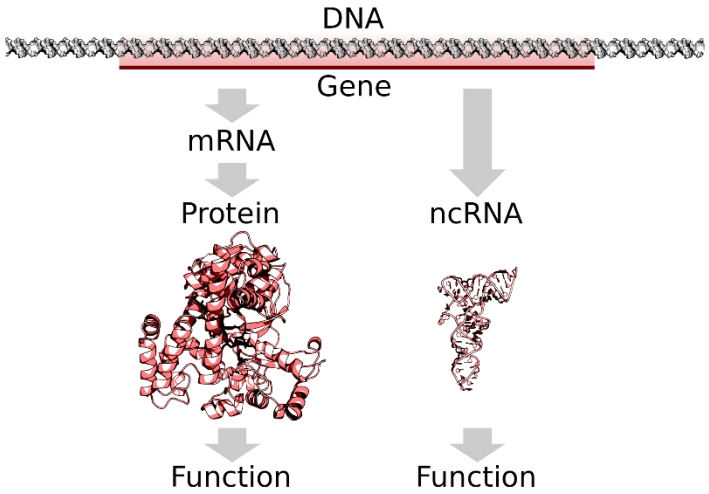
- Minimal or no organ malformations
- Transitory feeding difficulties
- No infections
- Mild intellectual impairment
- Behavioural abnormalities (sometimes severe!)

In Germany there are many less severely affected patients

Determination of severity

- Amount of residual DHCR7 enzyme activity
- Type of mutation

# Some basics on genetics




mons.wikimedia.org/w/index.php?curid=39441809

**Missense mutation:**

GAAGCCAUG → Glu – Ala – Met

GAAGUCAUG → Glu – Val – Met

**Insertion:**

GAAGCCAUG → Glu – Ala – Met

GAAGCUCAUG → Glu – Ala – His - …..

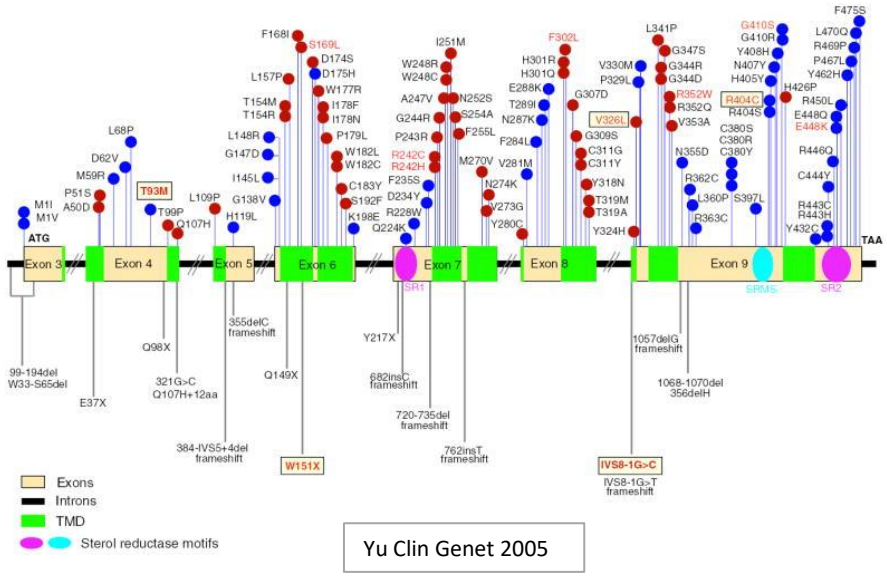
**Deletion:**

GAAGCCAUGA → Glu – Ala – Met

GAAGCAUGA → Glu – Ala – Stop

# SLOS genetics

- *DHCR7* gene maps to chromosome 11q13.2–13.5
- Consists of nine exons
- >200 different pathogenic *DHCR7* variants
- Most common mutation c.964–1G>C
- disrupts the joining of exons 8 + 9
- insertion of 134 nucleotides
- “Nonsense” mutation
- Complete loss of enzyme activity

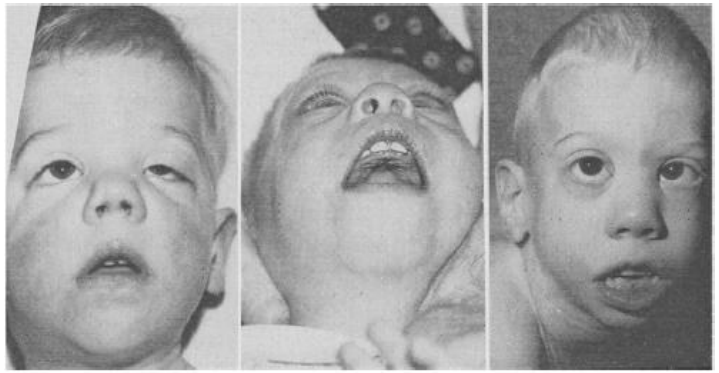



Yu Clin Genet 2005

Moebius Proc Natl Acad Sci 1998; Waterham Am J Med Genet C 2012; Witsch-Baumgartner Am J Human Genet 2000; Ciara Clin Genet 2004;

# SLOS – craniofacial characteristics

- Microcephaly – small head
- Ptosis – drooping of upper eylids
- Anteverted nostrils
- Microretrognathia – small and recessed jaw
- Bitemporal narrowing
- High arched palate
- Midline cleft palate
- Tent-shaped mouth
- Low set ears



*A newly recognized syndrome of multiple congenital anomalies*

*Three unrelated male children have been found to have a strikingly similar pattern of multiple congenital anomalies which suggests a common etiology. In addition to relative microcephaly with mental retardation and hypertonicity, these patients have incomplete development of the external genitals and abnormalities of the face, hands, and feet. Congenital pyloric stenosis was present in two of them. No chromosomal abnormality was found and the cause remains obscure though the apparent occurrence of the same condition in a deceased sibling of one of the patients suggests a genetic determination.*

David W. Smith, M.D.,* Luc Lemli, M.D., and John M. Opitz, M.D.

MADISON, WIS.

# SLOS – skeletal abnormalities

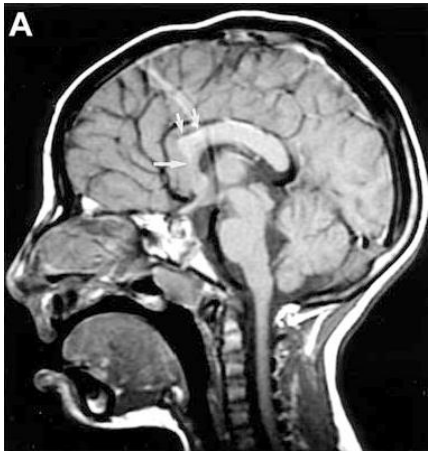
- Syndactyly toes 2/3
- Postaxial polydactyly
- Short, proximally placed thumbs
- Clinodactyly/brachydactyly

- Various foot deformities
- limb shortening

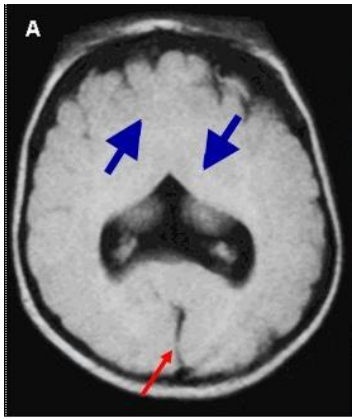
# SLOS – CNS malformations

- Corpus callosum agenesia / hypoplasia
- Enlarged ventricles
- Cerebellar hypoplasia
- Disturbed neuronal migration
- Various forms of holoprosencephaly

- Structural epilepsy is possible, however, SLOS is not typically associated with seizures




Caruso et al. Neuroradiology 2004




Solomon et al. GeneReviews 2000

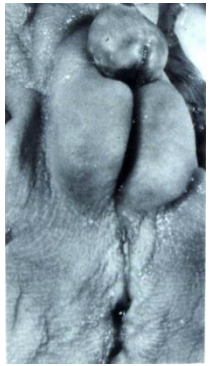
# SLOS – genital anomalies

Male patients

- Maldescensus of testicles
- Hypospadias
- Micropenis
- Genital ambiguity

Female patients

- Mostly normal
- Hypoplasia labia majora and minora
- Puberty premature / delayed
- Normal fertility – one pregnancy published

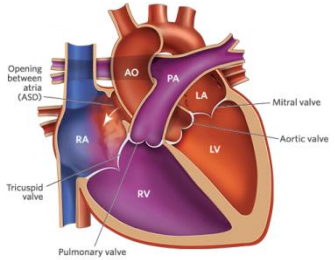


Ellingson Clin Genet 2014

# SLOS – cardiovascular anomalies

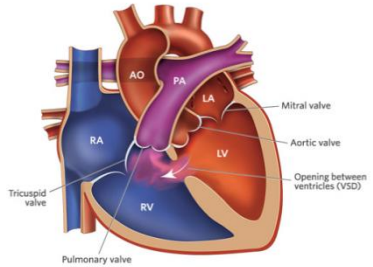
Frequently endocardial cushion defects

- Atrial septal defect
- Ventricular septal defect
- Patent ductus arteriosus (at term)




Hypoplastic left heart

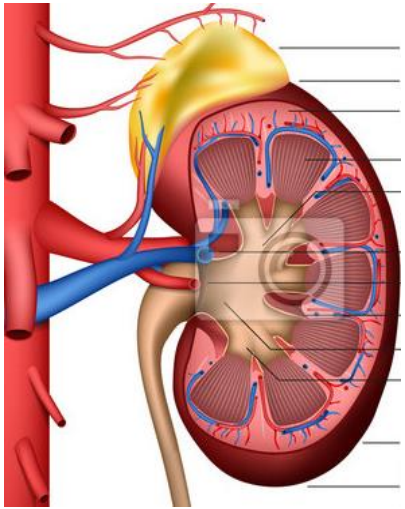
Persistent pulmonary hypertension



# SLOS – renal and adrenal problems

**Kidney and urinary tract**

- Renal hypo-/ aplasia
- Renal cysts
- Hydronephrosis
- Renal ectopia
- Urinary tract abnormalties
- Arterial hypertension



**Adrenal function**

- Severely affected patients: adrenal insufficiency
- Abnormal cortisol response to stress (surgery, infections)
- Adrenal insufficiency can lead to death

Bianconi Am J Med Genet 2011; Donoghue J Ped Endocr Metab 2018

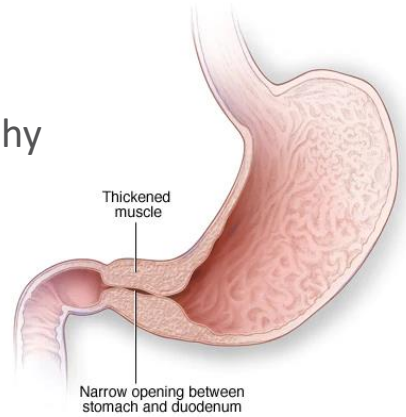
# SLOS – gastrointestinal problems

**Structural problems**

- Pyloric stenosis
- Aganglionosis (Hirschsprung disease)
- Anal atresia

**Hepatic complications**

- Cholestatic hepatopathy
- Liver cirrhosis




**Functional problems**

- Feeding difficulties
- Intestinal dysmotility (frequent vomiting)
- Food allergies
- Oral hypersensitivity
- Swallowing problems
- **Tube feeding often necessary to ensure adequate caloric intake**

# SLOS - nutrition

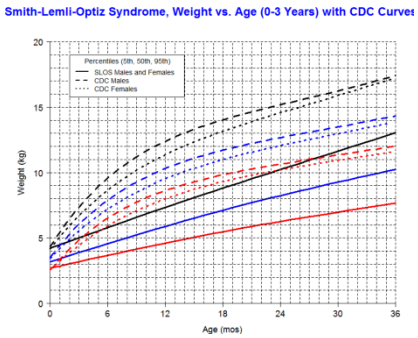
https://www.spiegel.de

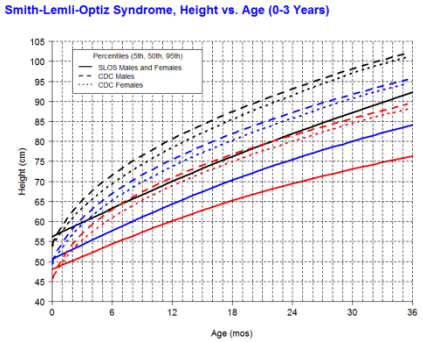
**Caloric intake**

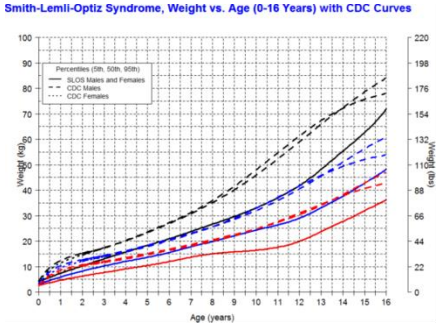
- Normal weight: according to reference values for healthy children
- Weight < P3: add 20 %
- Weight > height: reduce 10-30 %

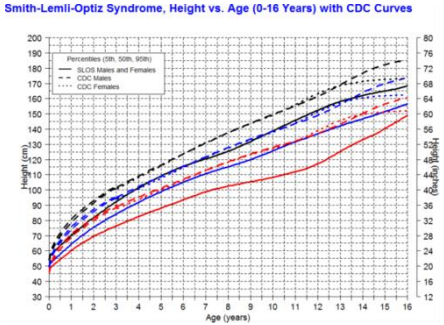
# SLOS – growth failure

- 48 male, 35 female SLOS patients, 0-16 y
- Growth – 2 SD
- Linear opposed to exponential growth in early childhood
- Supplemental nutrition will not result in improved growth




Lee Am J Med Genet A 2012

# Development and behavioural abnormalities

**Development**

- Delayed psychomotor development
- Gross motor development more affected than fine motor
- Expressive language more impaired than receptive language
- Cognitive impairment:
  - 1/3 severe to profound intellectual disability

**Behaviour**

- Hyperactivity
- Hypersensitivity to external stimuli
- Impulse control disorder
- Aggressive and autoagressive behaviour
- Self-injury
- Autistic features (51-71 %)
- Abnormal sleep pattern
  - Sleep apnea

Thurm J Neurodev Disord 2016; Diaz-Stransky Am J Med Genet C 2012

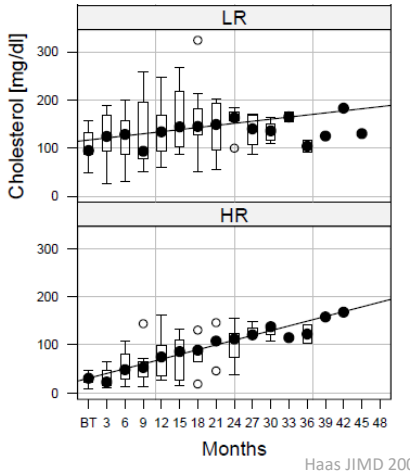
# SLOS treatment

# Cholesterol supplementation

- Blood cholesterol concentration ↑
- Weight and growth ↑
- Photosensitivity ↓
- Frequency of infections ↓
- Tactile defensiveness ↓
- Improves behaviour (?)

- does not pass blood-brain barrier, no effect on intrinsic cognitive abilities

Serum cholesterol concentration




n=14

n=9

Haas JIMD 2007

Haas JIMD 2007; Irons Am J Med Genet 1997; Nwokoro Am J Med Genet 1997; Azurdia Br Dermatol 2001; Tierney Am J Med GenetA 2010; Sikora: J Pediatr 2004

# Cholesterol supplementation

- Dosage
  - Children 100-200 mg/kg/d
  - Adults 3-4 g/d (higher dosages are not absorbed)
- Preparation:
  - Egg yolks (1 yolk = 180 - 220 mg cholesterol)
  - Pure powder or crystalline cholesterol (in Germany not approved for clinical use)
    - Sonic Cholesterol seems to be a suitable product (no personal experience)
  - Cholesterol preparations (enriched with sucrose or fat)
  - Powder should be dissolved in fat (butter, cream, oil) to ensure enteral absorption
  - Tube feeding: dissolve powder in oil or cream and mix this with part of the tube feed.

https://magazin.bodychange.de

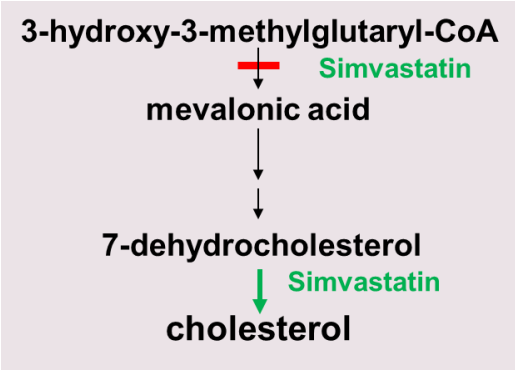
Sucrose
Cholesterol

Cholesterol
Soy oil
Vitamin C + E

Cholesterol

# Simvastatin

- Passes blood-brain-barrier
- HMG-CoA reductase ↓
- *DHCR7* expression ↑
- Cell culture: Rapid death of cells with null mutations
- 7-DHC ↓, (7+8-DHC)/Chol ↓
- Irritability ↓
- Side effects: CK and liver enzymes ↑
- Deterioration of behaviour and sleep problems




Jira: J Lipid Res 2000; Wassif: Mol Genet Metab 2005; Haas: JIMD 2007; Wassif: Genet Med 2017

# Heidelberg Simvastatin protocol

https://www.dr.maxi.com

- Only in mildly/moderately affected patients - ratio (7+8-DHC)/Cholesterol < 1
- Normal CK and liver enzymes
- Start with 0.5 mg/kg b.i.d, increase to 1 mg/kg/d after 4 weeks if CK and liver enzymes are still normal
- Maximal dosage: 30-40 mg/d
- Reliable contraception in postpubertal girls

# Treatment of behavioural and sleep problems

- Cholesterol supplementation may improve behaviour
- Behavioural interventions may help in patients with mild/moderate cognitive impairment
- Antipsychotic medication (risperidone, melperone) may be necessary in severe cases

**Sleep**

- Melatonin is effective in pediatric patients
- No deterioration of sterol pattern seen in SLO patients

# Antioxidants

https://www.wir-essen-gesund.de

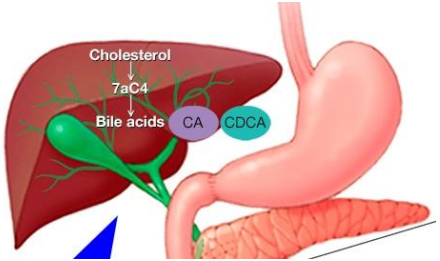
- 7-DHC is a very reactive molecule, which is easily converted to oxysterols
- Oxysterols promote cell death, activate inflammation, modulate immune responses
- Oxysterols lead to eye problems in SLOS rat model
- Cholesterol-rich diet enhanced with vitamin C+E prevents eye problems in rats

- Oxysterols are elevated in blood of human SLO patients
- Vit A, C, E + CoQ10 reduce 7-DHC oxysterols in human skin cells

- Clinical trial in Colorado recruiting since 2008 (ClinicalTrials.gov Identifier: NCT01773278)

Korade J Lipid Res 2010; Elias Arch Ophtalmol 2003; Garry: Doc Ophtalmol 2010; Liu: J Lipid Res 2013; Korade: Biol Psychiatry 2014

# Bile acids

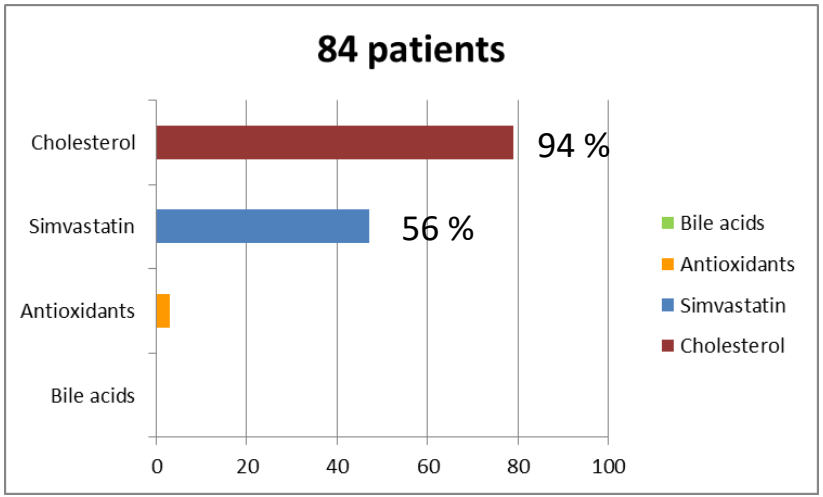



- Necessary for digestion of fat and resorption of fat soluble vitamins
- Reduced bile acid production in severely affected patients
- Normal bile acid synthesis in mildly affected patients
- No evidence for fat malabsorption or deficiency of fat soluble vitamins in SLO patients
- Supplementation not generally recommended in SLOS

- Cholic acid supplementation  may increase cholesterol and reduce DHCs
- Clinical trial not yet recruiting (ClinicalTrials.gov Identifier: NCT03720990)

Natowicz Am J Med Genet 1994
Steiner J Lipid Res 2000
Kelley J Med Genet 2000
Irons Am J Med Genet 1997

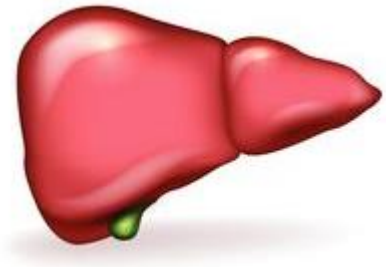
# Which kind of **medication** do SLOS patients receive in Heidelberg?



# Experimental therapeutic options

**Liver transplantation**

- 19 m old SLO patient, liver cirrhosis
- living-donor split liver transplant from his uncle
- 34 m after transplant: improved fine and gross motor and social skills



**Gene therapy - intravenous**

- Gene therapy using a recombinant AAV vector in mouse model
- Copies of gene detectable in liver, loss of vector copies over several weeks
- Reduction of serum 7-DHC, no effect on brain

**Gene therapy - intrathecal**

- Partial restoration of sterol levels in CNS, but not in periphery

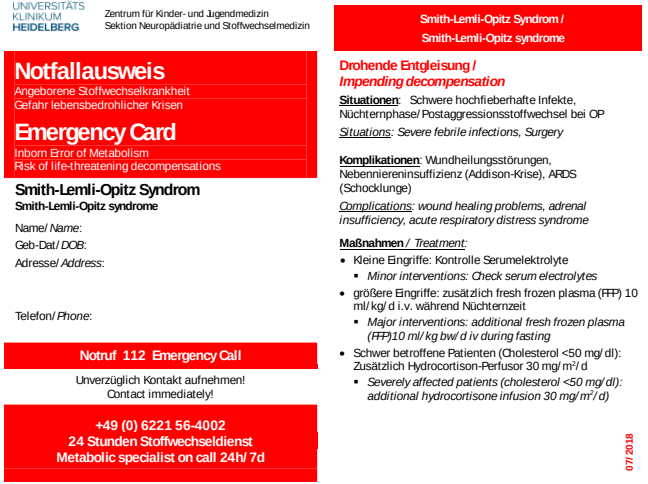
Ertugrul Exp Clin Transplant 2018; Matabosch J Steroid Biochem Mol Biol 2010; Pasta Mol Genet Metab Rep 2015

# Emergency protocol – illness and surgery

**Problems**

- Risk for adrenal insufficiency
- Airway management (micrognathia, palatal anomalies)
- Cholesterol can only be given perorally

- Emergency regimen depending on severity and intervention
- Consider steroids
- Fresh frozen plasma (FFP) may be a source of cholesterol



UNIVERSITÄTS KLINIKUM HEIDELBERG

Zentrum für Kinder- und Jugendmedizin
Sektion Neuropädiatrie und Stoffwechselmedizin

**Notfallausweis**
Angeborene Stoffwechselkrankheit
Gefahr lebensbedrohlicher Krisen

**Emergency Card**
Inborn Error of Metabolism
Risk of life-threatening decompensations

**Smith-Lemli-Opitz Syndrom**
**Smith-Lemli-Opitz syndrome**

Name/ *Name*:
Geb-Dat/ *DOB*:
Adresse/ *Address*:

Telefon/ *Phone*:

**Notruf 112 Emergency Call**

Unverzüglich Kontakt aufnehmen!
Contact immediately!

**+49 (0) 6221 56-4002**
**24 Stunden Stoffwechseldienst**
**Metabolic specialist on call 24h/ 7d**

**Smith-Lemli-Opitz Syndrom /**
**Smith-Lemli-Opitz syndrome**

**Drohende Entgleisung /**
***Impending decompensation***

**Situationen**: Schwere hochfieberhafte Infekte, Nüchternphase/ Postaggressionsstoffwechsel bei OP

*Situations: Severe febrile infections, Surgery*

**Komplikationen**: Wundheilungsstörungen, Nebenniereninsuffizienz (Addison-Krise), ARDS (Schocklunge)

*Complications: wound healing problems, adrenal insufficiency, acute respiratory distress syndrome*

**Maßnahmen** / *Treatment:*

- Kleine Eingriffe: Kontrolle Serumelektrolyte
  - *Minor interventions: Check serum electrolytes*
- größere Eingriffe: zusätzlich fresh frozen plasma (FFP) 10 ml/ kg/ d i.v. während Nüchternzeit
  - *Major interventions: additional fresh frozen plasma (FFP)10 ml/ kg bw/ d iv during fasting*
- Schwer betroffene Patienten (Cholesterol <50 mg/ dl): Zusätzlich Hydrocortison-Perfusor 30 mg/ m²/ d
  - *Severely affected patients (cholesterol <50 mg/ dl): additional hydrocortisone infusion 30 mg/ m²/ d)*

07/ 2018

Kelley J Med Genet 2000
Boctor Ann Clin Lab Sci 2014

# Need to learn more

- SLOS - still many uncertainties:
- What is the long-term outcome (40-60-80 years)?
- mild phenotypes
- What is the optimal therapy for which patient?

- Necessity to collect patients of many different centers in European registry

Thank you for your attention!