CHILDREN'S RESEARCH CENTER (CRC)

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Niemann Pick C:
Die oft lange nicht erkannte lysosomale Speicherkrankheit: typische Fallberichte

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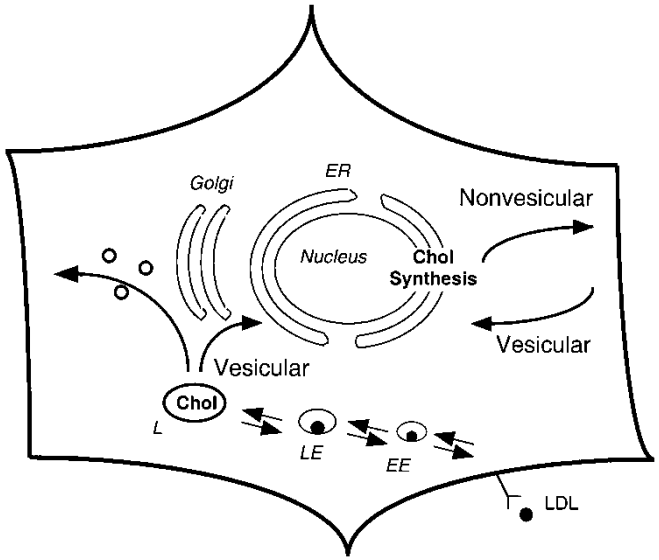
Niemann–Pick disease type C (NPC)

- Dr. med. A. Niemann in 1914 „*ein unbekanntes Krankheitsbild mit Neurodegeneration und Hepato-splenomaglie*“
- Pathology by Pick in 1933 „*Retikuloendotheliose*“
- Classification 1961 by Crocker (A, B, C)
- Prevalance 1:150,000
- autosomal recessive
- fatal neurovisceral lysosomal lipid storage disorder
- Biochemically and phenotypically different from Niemann–Pick types A and B, lysosomal sphingo-myelinase deficiency

NP-C

- Abnormal intracelluar lipid trafficing/transport
  - accumulation in the endosomal/lysosomal



Synthesis
Membran recycling

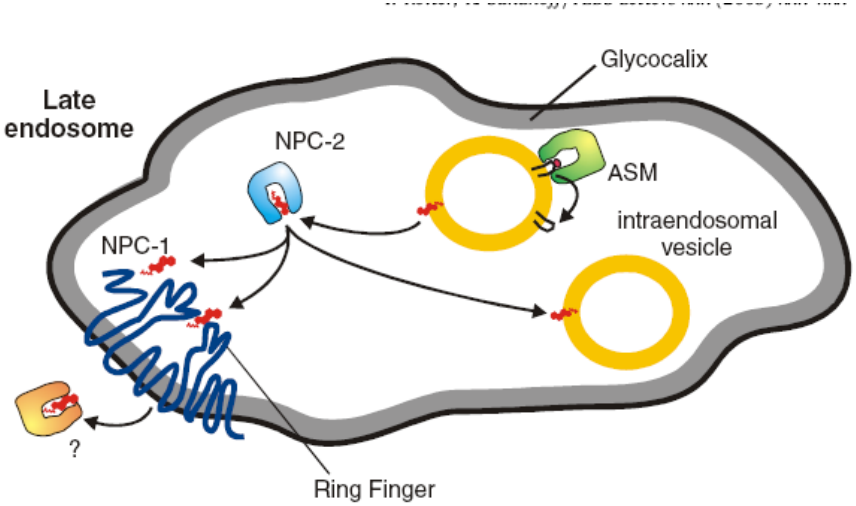
Lipoprotein uptake

- Complex lysosomal lipid storage disease
  - Storage involve several lipids including:
    - » unesterified cholesterol
    - » Glycosphingolipids: GM2 and GM3 gangliosides in the central nervous system
    - » Glycolipids

Molecular basis

- Consequence of a defect in two different genes

  - NPC1 (95%)
    - 18q11
    - Transmembraneus Protein
  - NPC2 (5%)
    - 14q24.3
    - Small soluble Protein
    - Lysosomal lumen



Coordinate two close step at the same pathway
Cellular postlysosomal/LER cholesterol transport and other cargo
Can not replace each another

Characteristic clinical signs and symptoms in NP-C, by age at onset.

Age at onset	Systemic manifestations	Neurological manifestations
Pre-/peri-natal period (⩽3 mo)	Fetal hydrops Hepatosplenomegaly Fetal ascites with or without persistence after birth Prolonged cholestasis (frequent) Hepatosplenomegaly Respiratory failure Hepatic failure	Usually not recognized
Early-infantile period (3 mo to <2 yrs)	Isolated hepatosplenomegaly or Hepatosplenomegaly	Delayed developmental motor milestones Central hypotonia Hearing loss VSGP[a] (usually not recognized)
Late-infantile period (2 to <6 yrs)	Isolated organomegaly or Organomegaly (usually present)	Frequent falls, clumsiness Progressive ataxia, dystonia, dysphagia, dysarthria Central hypotonia Hearing loss Seizures (partial or generalized) Cataplexy VSGP[a] (usually present)
Juvenile (classical) (6–15 yrs)	Isolated organomegaly or Organomegaly (not always present)	School failure, learning disability Behavioral problems Frequent falls, clumsiness Progressive ataxia, dysarthria, dystonia, dysphagia Myoclonus Cataplexy Seizures (partial and/or generalized) VSGP[a] (usually present)
Adolescent and adult (>15 yrs)	Organomegaly (not always present) or Isolated splenomegaly in adults has been described in exceedingly rare cases	Clumsiness Cataplexy Psychiatric signs[b] Cognitive decline, dementia, learning disability VSGP[a] (usually present) Slowly progressing motor symptoms[c] Myoclonus Seizures (partial and/or generalized)

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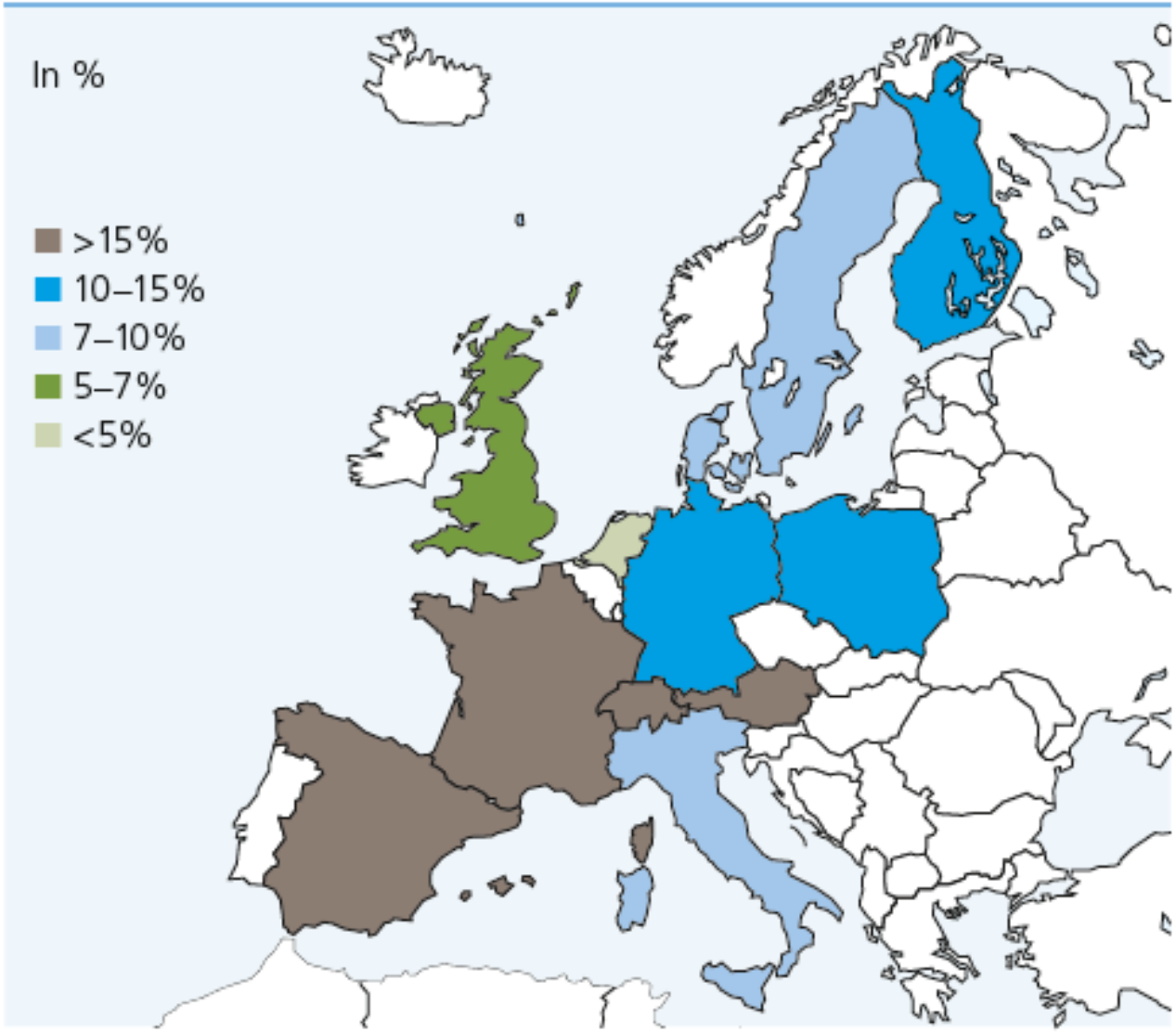
Anteil Patientinnen und Patienten, die aufgrund einer Fehldiagnose operiert wurden



Quelle: EURODIRS, 2009

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Anteil Fehldiagnosen NPC Schweiz

10 diagnostizierte Patienten in der Schweiz:

- 1 x Diagnose mit 2 Jahren v.a Leukämie
- 4 x Diagnose mit 12-19 Jahren
- 5 x Diagnose > 20 Jahre

Patientenkollektiv Schweiz

Neugeborenen	Hepato/	Stürze/	Konzentrations-	Progredienter
Ikterus	Splenomegalie	Ungeschickt	Störung	kognitiver Abbau und/oder psychiatrische Auffälligkeiten
6/10	5/10	6/10	9/10	8/10

Hörstörung 2/10
Vertikale Blickparese 6/10

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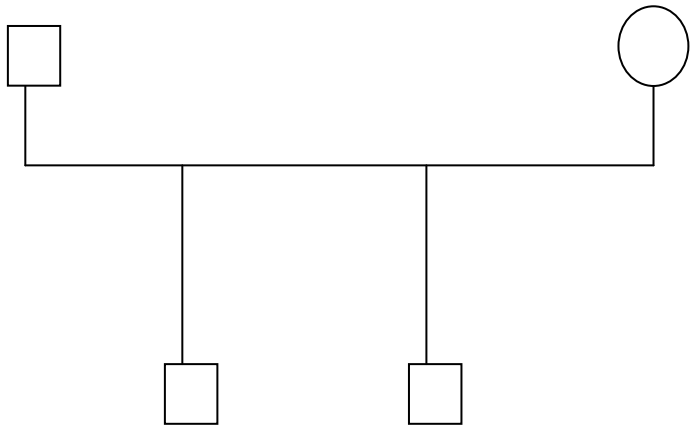
Diagnoseliste

- Demenz
- Neurodegeneratives Leiden
- Schwer reichende Funktionsstörungen
- Chorea Huntigton, M. Wilson, Fragiles X Syndrom, M. Gaucher, Tyrosinämie
- Leukämie
- …..

Familie B

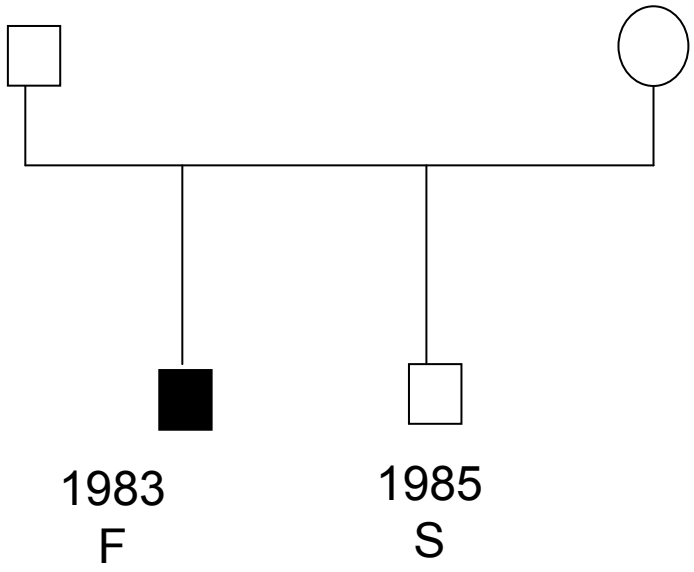


F+S: 1988 normale Entwicklung

F: 1988 Rezidivierende Infekte, Splenomegalie, Anämie Diagnose: ?

S: 1987 Hepatosplenomegalie, Anämie Diagnose: Cytomegalie

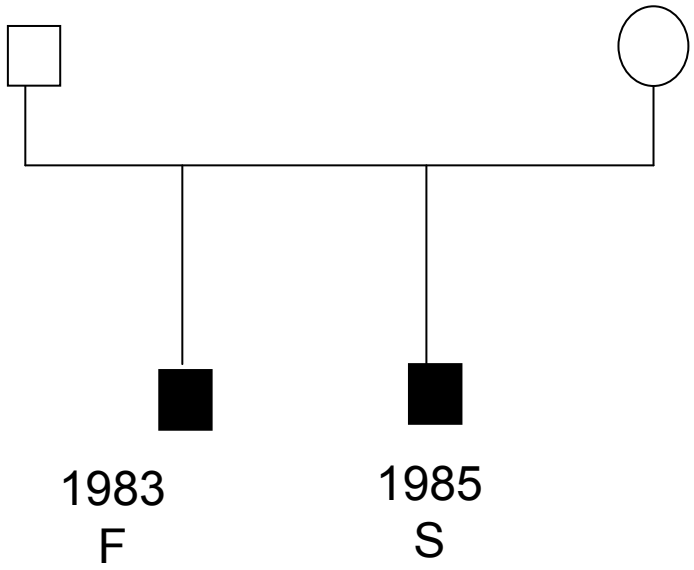
Fall



F: 1989 persitierende Splenomegalie
Enzymatik: saure Phosphatase ++
beta-Glucosidase --
Knochenmarkspunktion: vermehrte Retikulumszellen mit schaumig weiss-bis mittelblauem Plasma

Diagnose: M. Gaucher

Fall

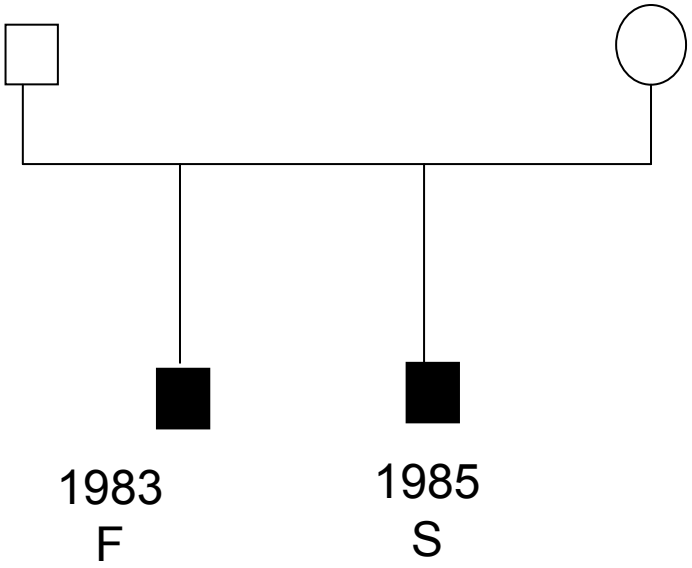


S: 1989 4 Jh
normale psychomotorische Entwicklung, Hepatosplenomegalie ??

1991 6 Jh Leistungsabfälle
KMP

Diagnose: M. Gaucher

Weiterer Verlauf



Schliesst obligatorische Schule normal ab
Berufslehre Probleme: Leistungsabfall
Tremor
Erhöhter Schlafbedarf

Langsam kontinuierlich Abwärts ab 13 Jj
Tremor
Chronisch Kopfschmerzen
Zunehmende Spastik
Pyschiatrische Probleme

Second Opinion 2001 (10 Jahre Später)

Second Opinion 2001

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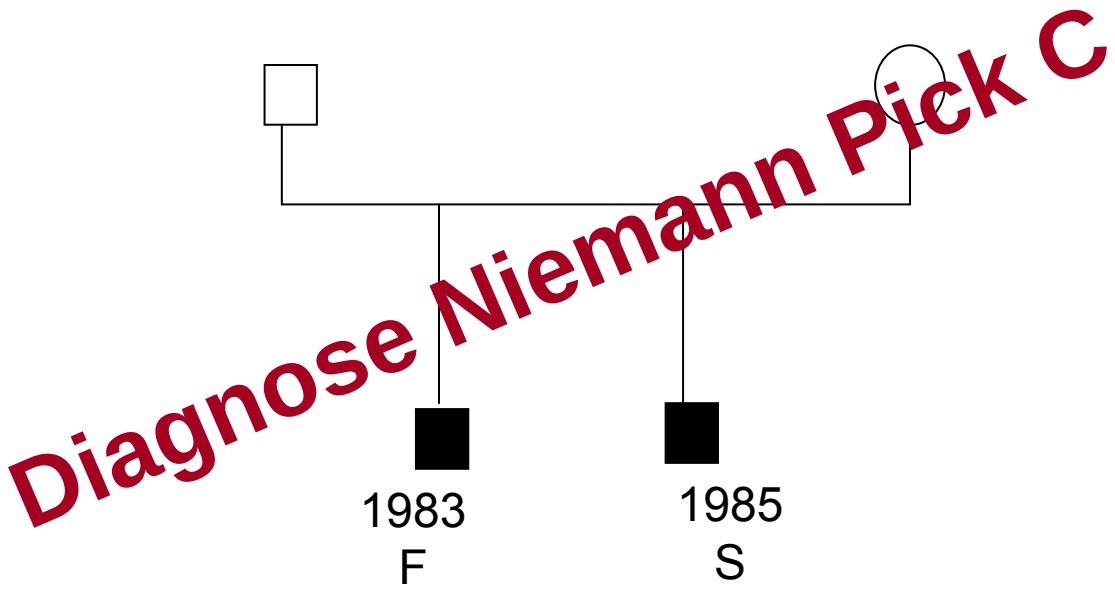

Splenomegalie
Spastische Komponente
Hyperreflexie
Subkloni
Cerebelläre Komponente
Dysarthrie
abnorme Diatochokinese
Supranukleäre vertikale Blickparese

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Spastische Komponente
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Dysarthrie
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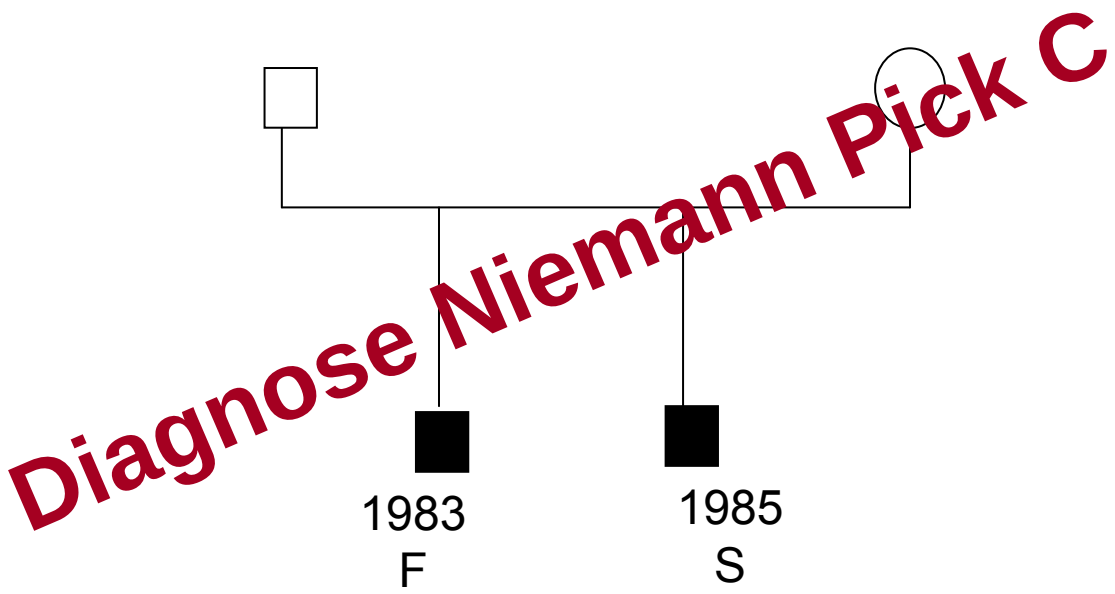
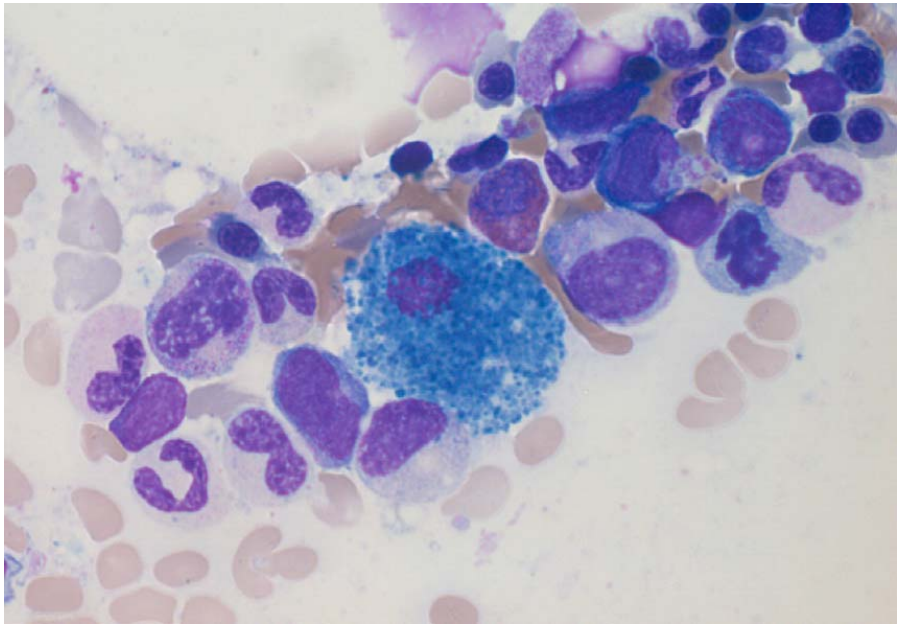
Diagnose 2001



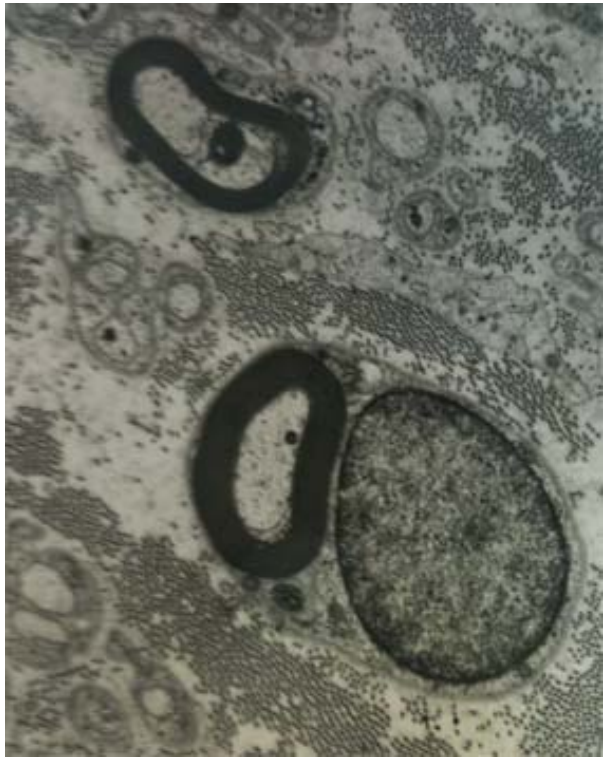
Start: Therapie Miglustat (Zavesca 2007)

Stabilisierung der Symptomatik bei beiden Brüder

Diagnostischer Delay bei Niemann Pick C



Konchenmarkausstrich
Sea-blue histiocytes
Schaumzellen



Elektronenmikroskopie (Haut)
pathognomische zytoplasmatische Einschlüsse

NP-C Diagnosis

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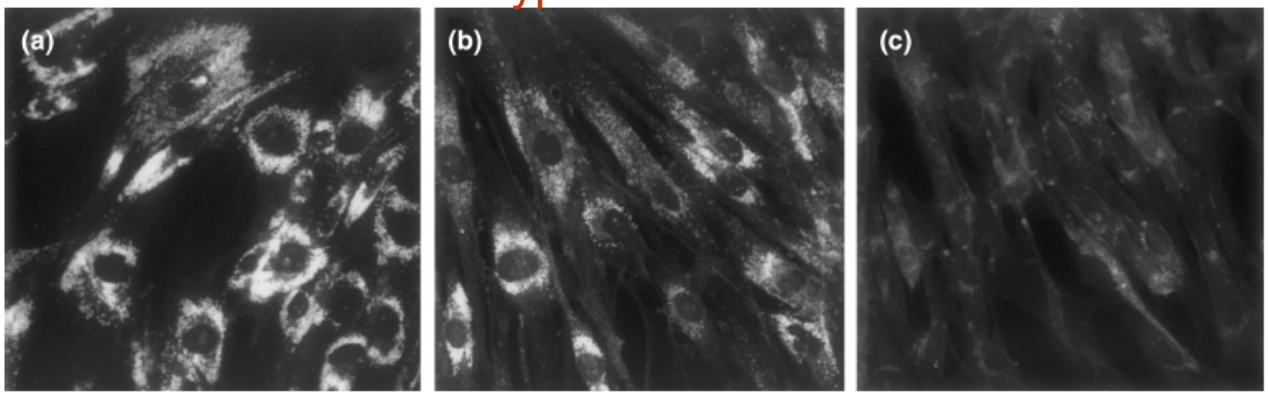
- No screening test in urine/blood reliable
- Chitotriosidase moderately elevated (10-20 fold)
- Foam Cells in BM (stain positive with filipin)
- Unesterified cholesterol accumulation in fibroblasts (filipin stain)
- Molecular analysis

Classical NP-C | atypical NP-C | normal



Vanier and Millat

Clin Genet 2003: 64: 269–281

NPC Suspicion Index

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Figure 1 Suspicion Index tool

Indicators	Signs and symptoms: Visceral	Score	Neurological	Score	Psychiatric	Score
Very strong 40 points per item			• Vertical supranuclear gaze palsy • Gelastic cataplexy	☐ ☐		
Strong 20 points per item	• Prolonged unexplained neonatal jaundice or cholestasis • Isolated unexplained splenomegaly (historical and/or current) with/without hepatomegaly	☐ ☐			• Pre-senile cognitive decline and/or dementia	☐
Moderate 10 points per item			• Ataxia, clumsiness or frequent falls • Dysarthria and/or dysphagia • Dystonia	☐ ☐ ☐	• Psychotic symptoms (hallucinations, delusions and/or thought disorder)	☐
Weak 5 points per item			• Acquired and progressive spasticity	☐	• Treatment-resistant psychiatric symptoms • Other psychiatric disorders	☐ ☐
Ancillary 1 point per item	• Hydrops fetalis • Siblings with fatal ascites	☐ ☐	• Hypotonia • Delayed developmental milestones • Seizure (partial or generalised) • Myoclonus	☐ ☐ ☐ ☐	• Disruptive or aggressive behaviour in adolescence and childhood	☐
Category scores	☐	+	☐	+	☐	

Category combination

40 points: Visceral & psychiatric
40 points: Visceral & neurological
20 points: Neurological & psychiatric

Visceral & psychiatric ☐ + Visceral & neurological ☐ + Neurological & psychiatric ☐

NP-C family relationship

40 points: Parent/sibling
10 points: Cousin

Parent or sibling with NP-C ☐ + Cousin with NP-C ☐

Risk Prediction Score ☐ = Sum of scores

Symptoms are scored according to their relative association with positive Niemann-Pick disease type C (NP-C) diagnosis. The combination of symptoms and the patient's family history together provide the prediction score.

Wijburg FA et al; *Neurology* 2012, 15;78(20

Development of a Suspicion Index to aid diagnosis of Niemann-Pick disease type C.

NPC Suspicion Index

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Risk prediction Score	
<40	**Low probability of having NP-C** Discount other possible causes first
40–69	**Moderate suspicion for NP-C** Follow up observation is required, re-examine carefully all signs in due time. Contact your nearest NP-C referral centre for further discussion
≥70	**High suspicion for NP-C** Refer to an NP-C centre for immediate testing for NP-C

Abklärungsschema

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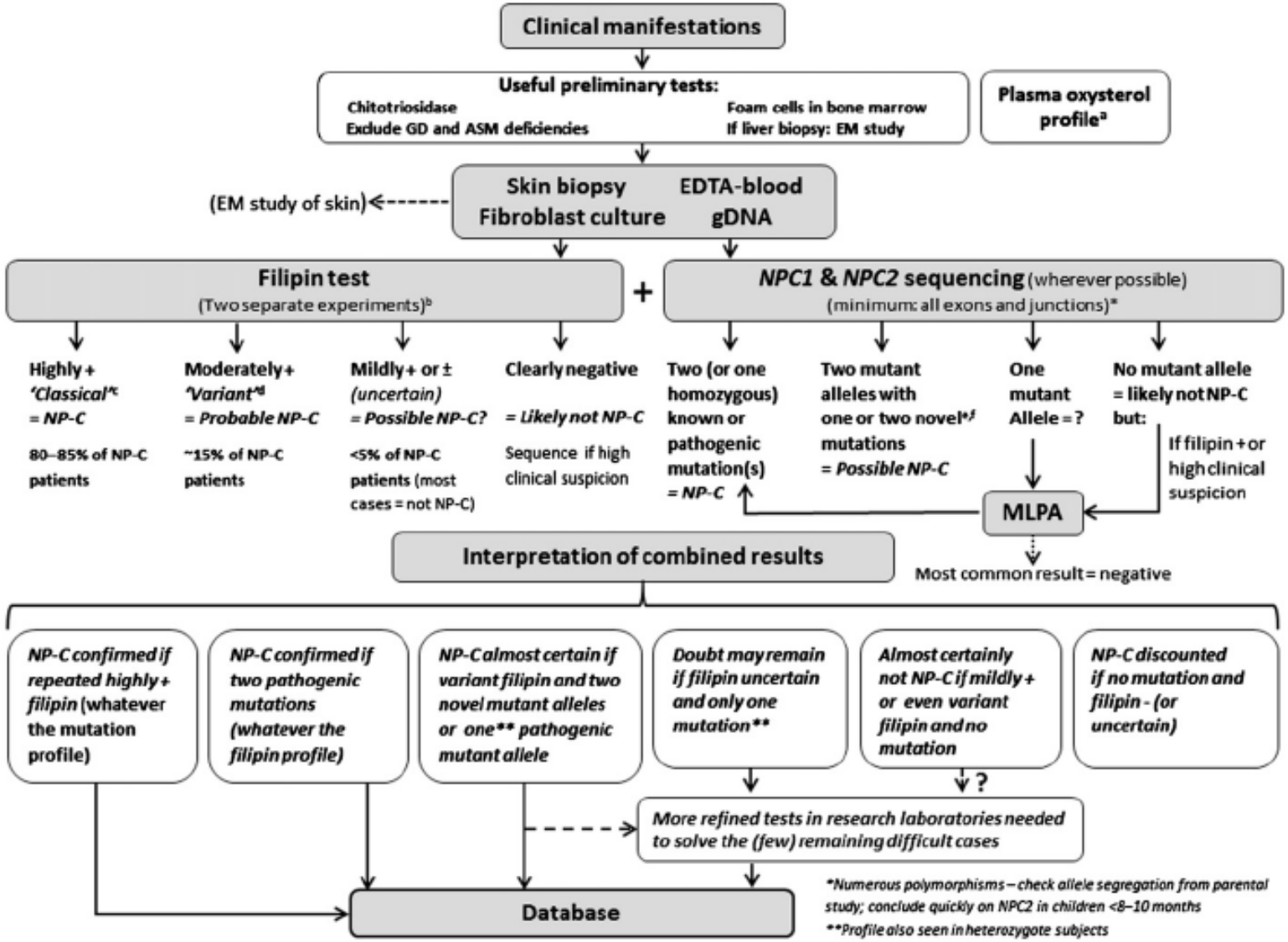

M.C. Patterson et al. / Molecular Genetics and Metabolism (2012)

Treatment for NP-C

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- no cure for NP-C
- palliative therapy
- Miglustat: a small iminosugar molecule that reversibly inhibits glucosylceramide synthase (glycosphingolipis)
- EMEA approved 2009
- Health Canada: approved 2010
- FDA : rejected 2010
- Swiss medic: awaiting approval 2010(?)

N-butyldeoxynojirimycin Miglustat

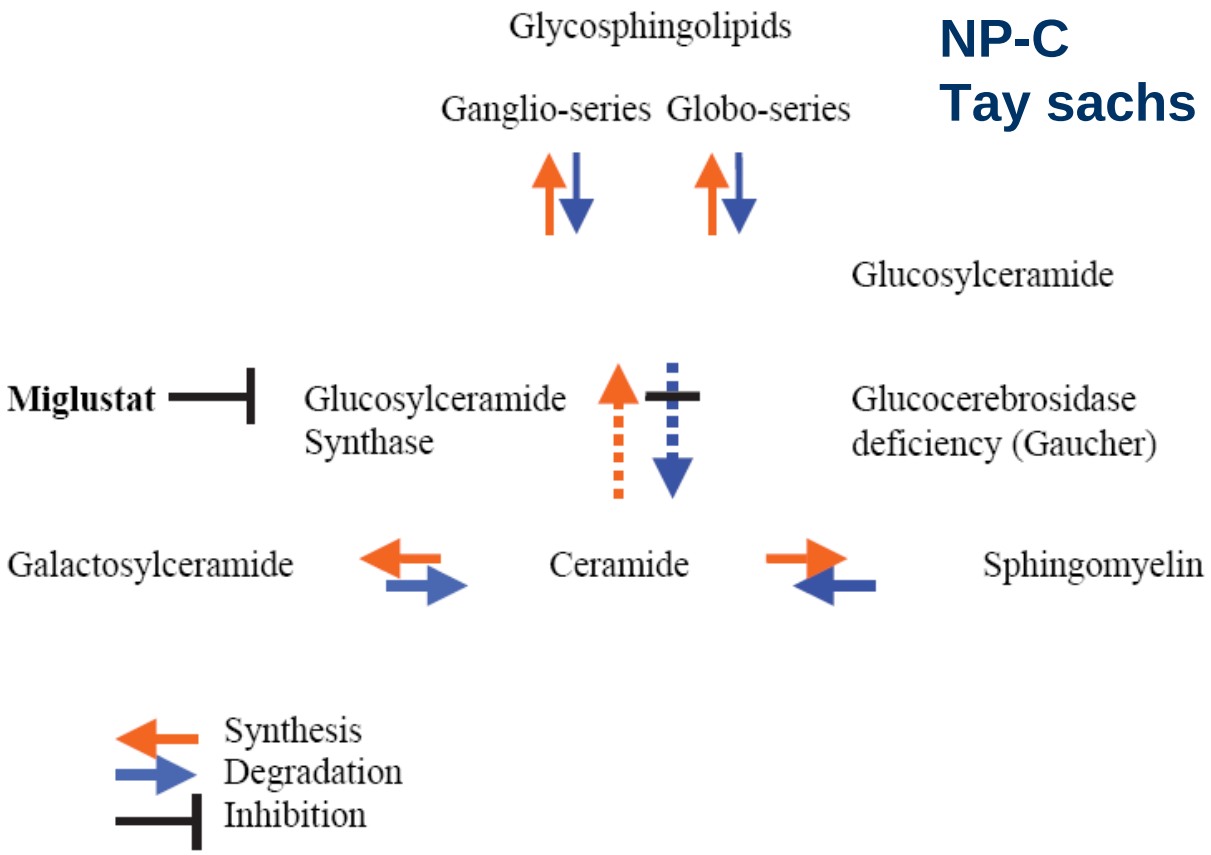


Figure 1 Inhibition of glucosylceramide synthesis with miglustat.

Review of miglustat for clinical management. *Therapeutics and Clinical Risk Management* 2008:4

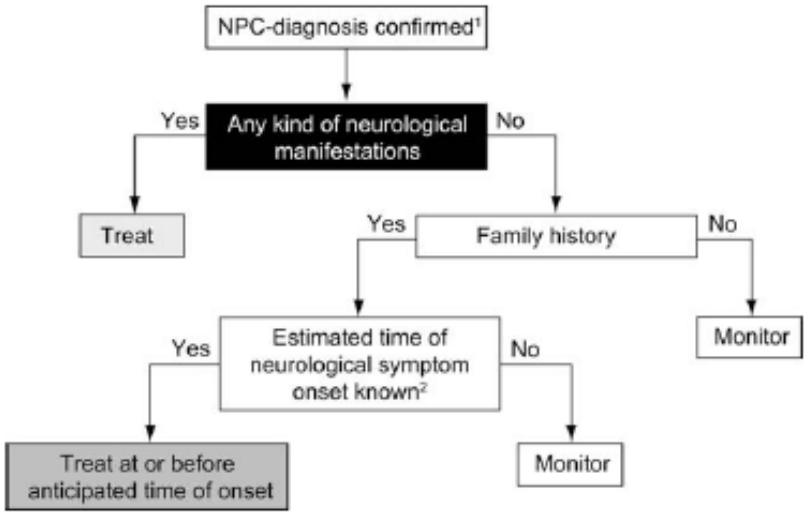
Whom to treat

not formally contraindicated in any of the patient types.

Immediately in patients with any type of neurological manifestations.

In patients who do not have neurological manifestations but for whom there is a known family history and disease course, treatment should be commenced at or before the anticipated time of neurological symptom onset

Patients with early-infantile onset NP-C, and those with severe dementia in the terminal stage of the disease are less likely to benefit from treatment with miglustat (case by case basis).



James E. Wraith et al / Molecular Genetics and Metabolism 98 (2009) 152–165

Disability rating scale

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Ambulation	Original score	Modified score	Language	Original score	Modified score
Normal	1	0	Normal	1	0
Autonomous ataxic gait	2	0.25	Mild dysarthria[d]	2	0.25
Outdoor assisted ambulation	3	0.5	Severe dysarthria[e]	3	0.5
Indoor assisted ambulation	4	0.75	Non-verbal communication	4	0.75
Wheelchair bound	5	1	Absence of communication	5	1
Manipulation	**Original score**	**Modified score**	**Swallowing**	**Original score**	**Modified score**
Normal	1	0	Normal	1	0
Slight dysmetria/dystonia[a]	2	0.33	Occasional dysphagia	2	0.33
Mild dysmetria/dystonia[b]	3	0.67	Daily dysphagia	3	0.67
Severe dysmetria/dystonia[c]	4	1	NG tube or gastric button feeding	4	1

Iturriaga C, Pineda M, Fernandez-Valero EM, Vanier MT, Coll MJ.
Niemann-Pick C disease in Spain: clinical spectrum and development of a disability scale. ***J Neurol Sci*** 2006;249(1):1-6.

Ambulation and manipulation

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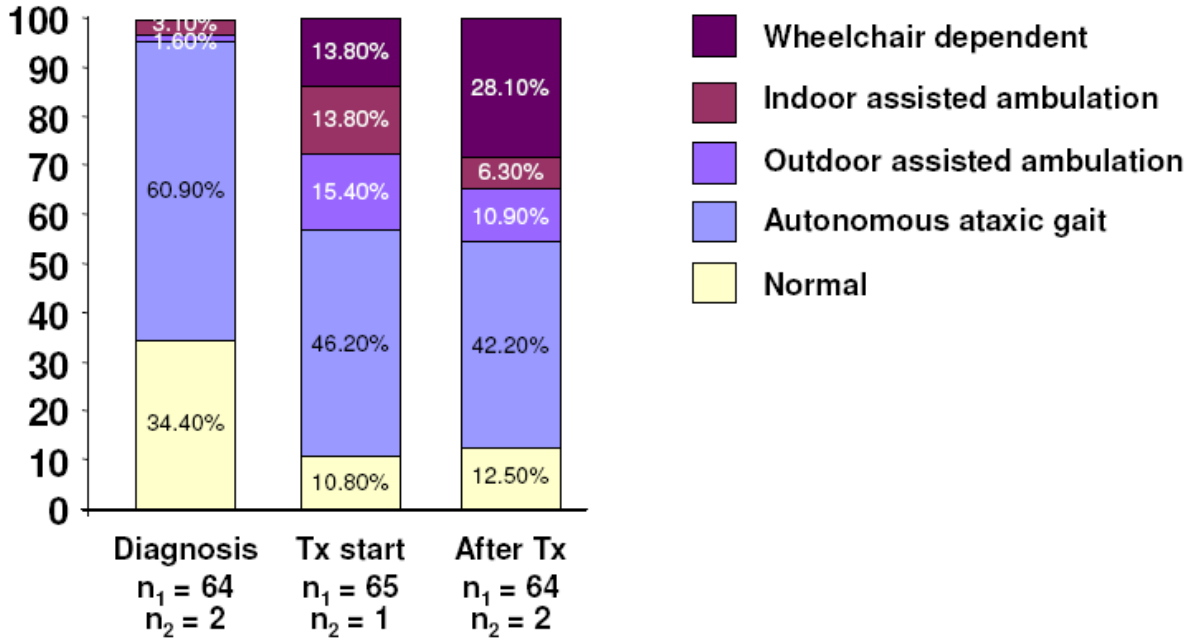
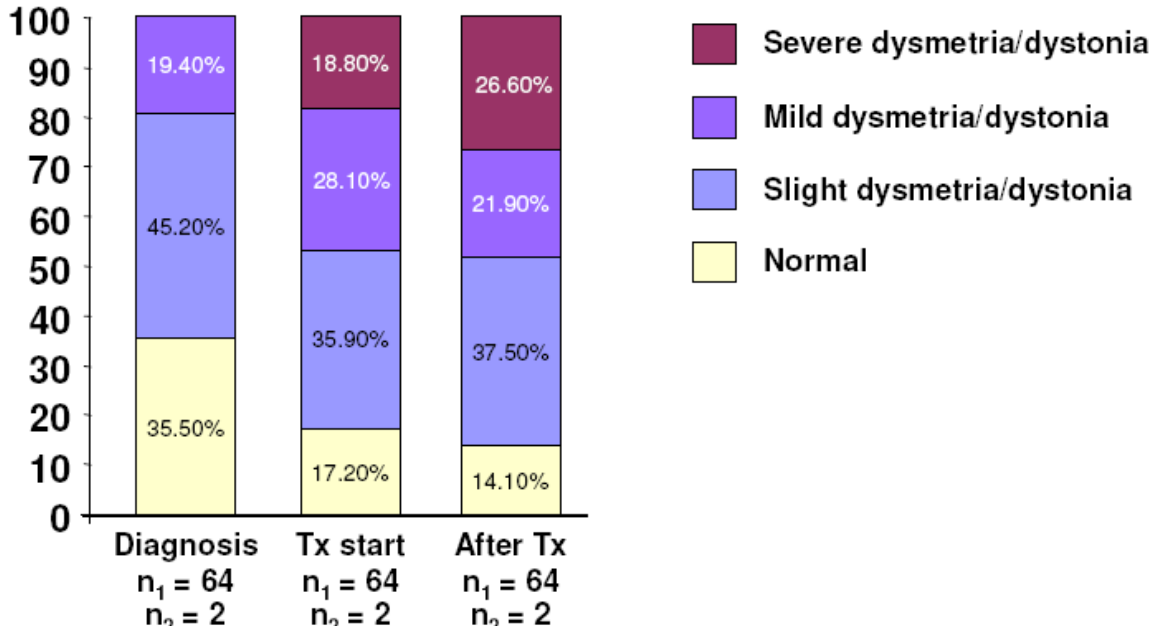
a)



b)



Language and Swallowing

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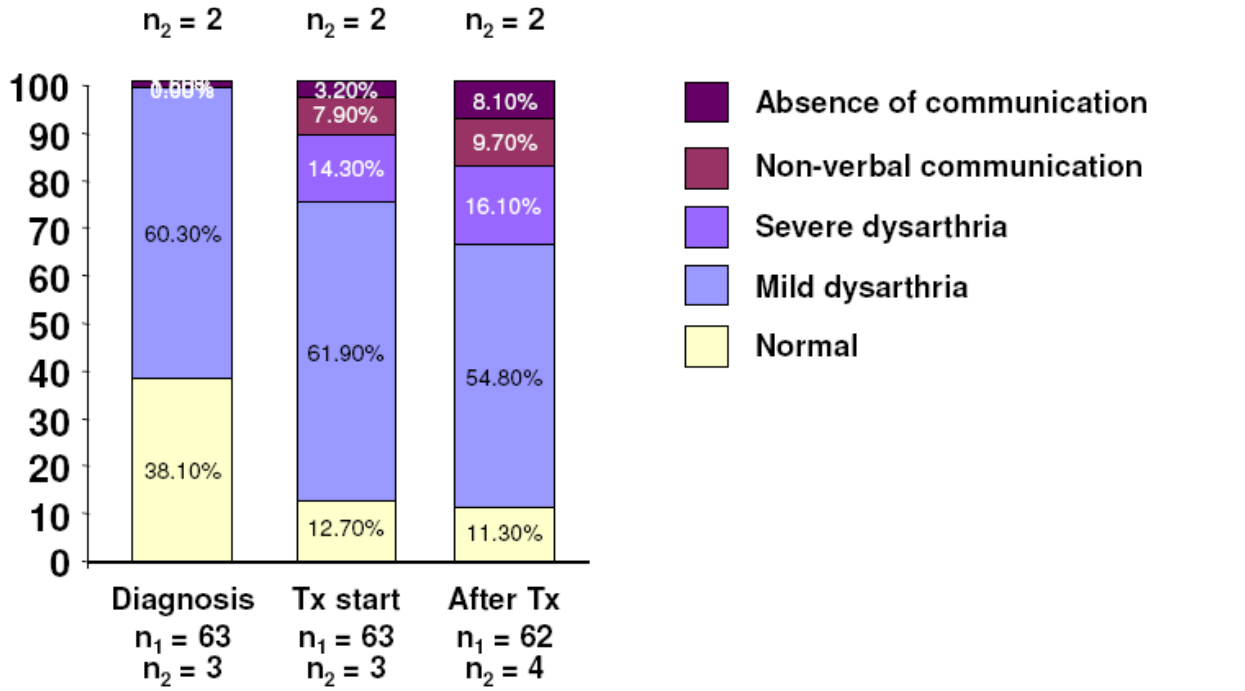
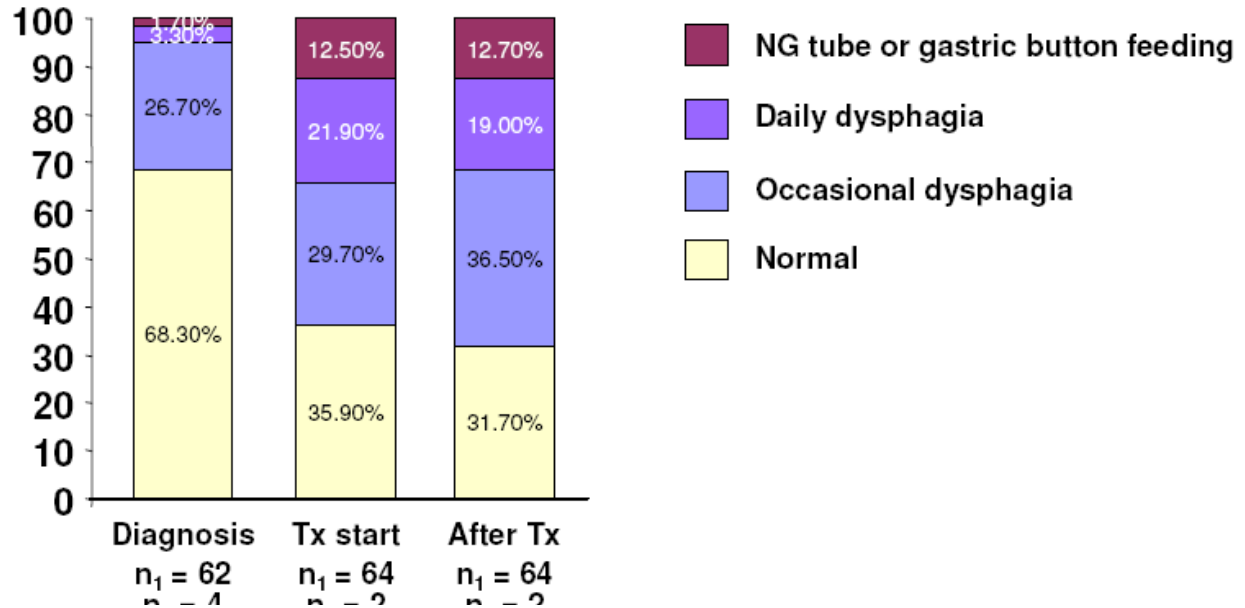
c)



d)



Take home message

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- NP-C heterogen; jede Altersgruppe
- Diagnosen hinterfragen
- Diagnostik prüfen
- Auf Spezifische Symptome achten:
  - Splenomegalie
  - Spastische Komponente
    - » Hyperreflexie
    - » Subkloni
  - Cerebelläre Komponente
    - » Dysarthrie
    - » Abnorme Diatochokinese
  - Supranukleäre vertikale Blickparese