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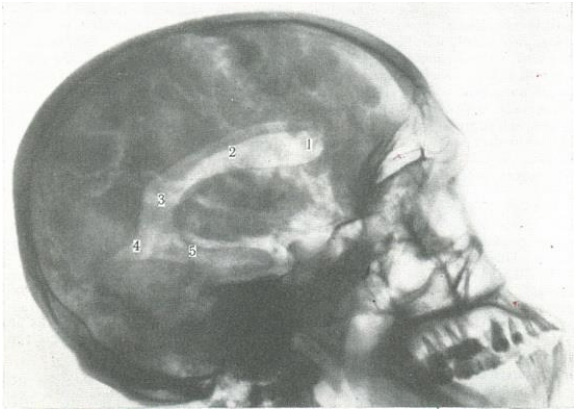
Lumbar Puncture
Practical Issues and Indications

Peter Born
Pediatric Neurology
Rigshospitalet, Copenhagen

Disclosures

None related to the contense of this presentation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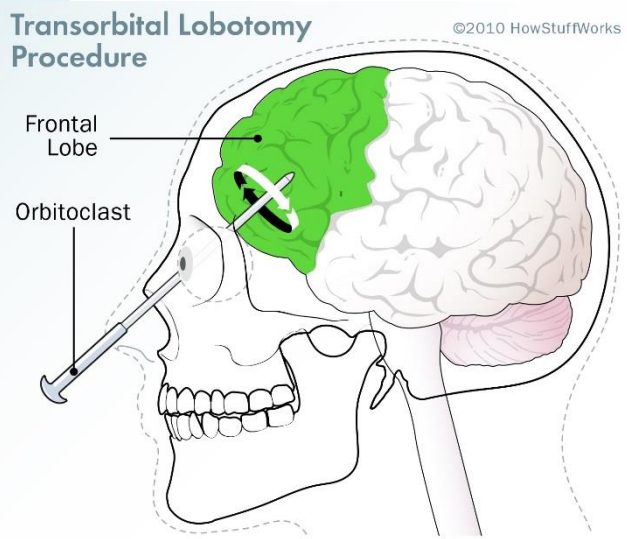
Transorbital Lobotomy Procedure
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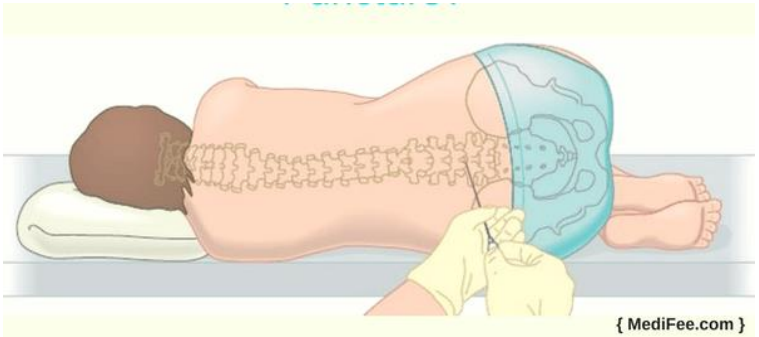
Frontal Lobe
Orbitoclast


{ MediFee.com }

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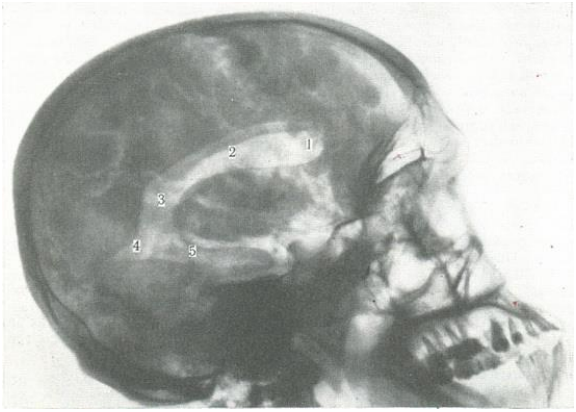

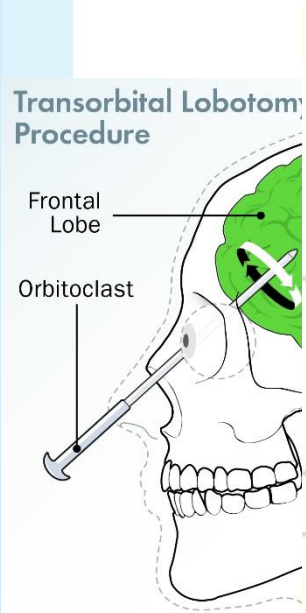

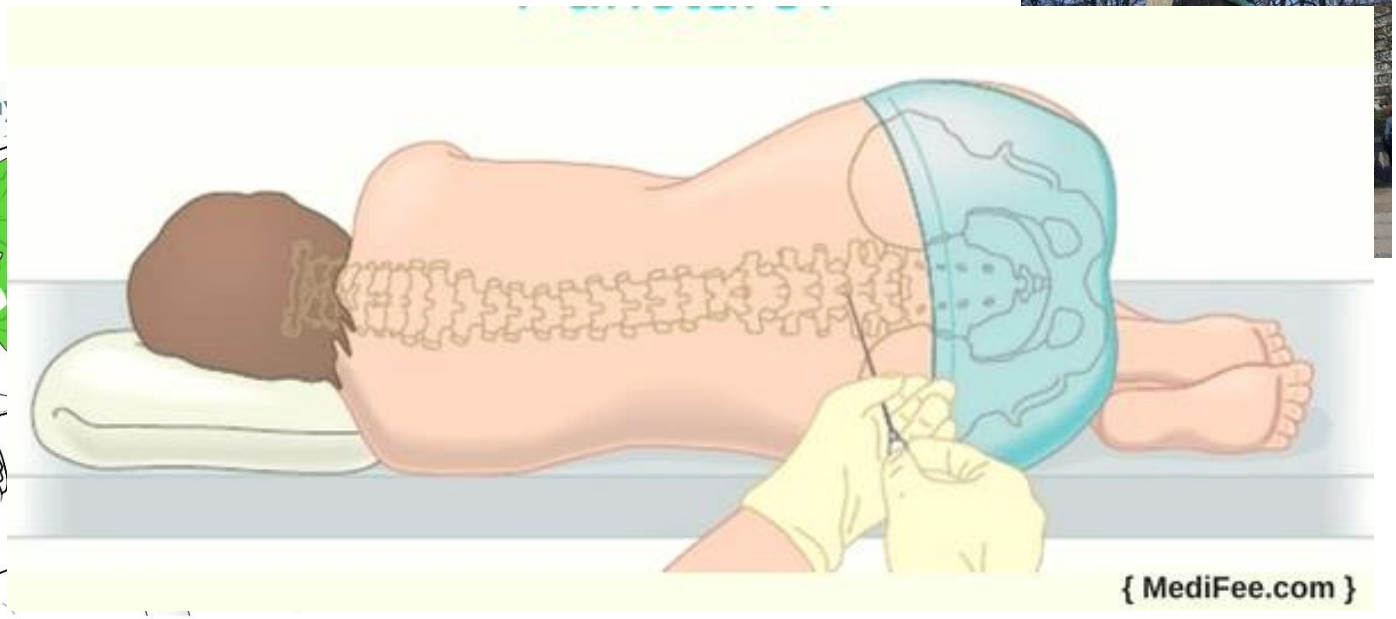

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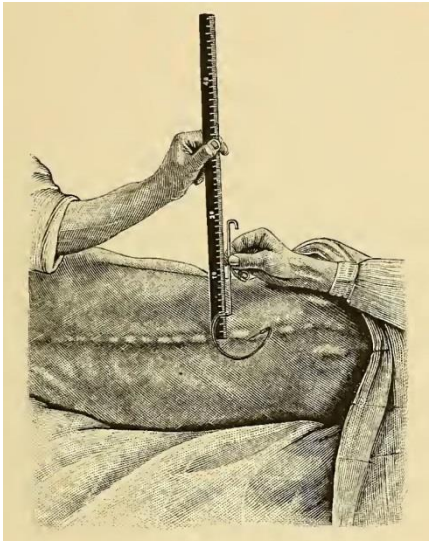
Thomas Willis
1621-75
”fluid altered in endemic fever”

Emanuel Swedenborg
1688-1772
”spiritous lymph”

Heinrich Irenaeus Quincke (1842 –1922)



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CSF volumes

- Adult static volume of 65-150ml –from 5y!
- Adult production ca 500ml daily -0,5ml/min
- Neonate 25ml/day production, static spinal volme ~2ml/kg, total ~4ml/kg (<15kg)
- CSF ultrafiltrate of plasma
- CNS capillaries lack fenestration and transport vehicles.
- 99% water + electrolytes, glucose, proteins, enzymes, antibacterial factors etc.

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CSF dynamics

- Produced in choroid plexus of ventricles
- Ventricles→ foramen Monroe →aquaeductus cerebri →for. Luschka and Magendii →subarachnoidal space
- Pulsatile flow
- Only 20% enters spinal subarachnoidal space- lumbar cistern 20ml
- CSF transit time appr 1 hour, replaced every 6 hours

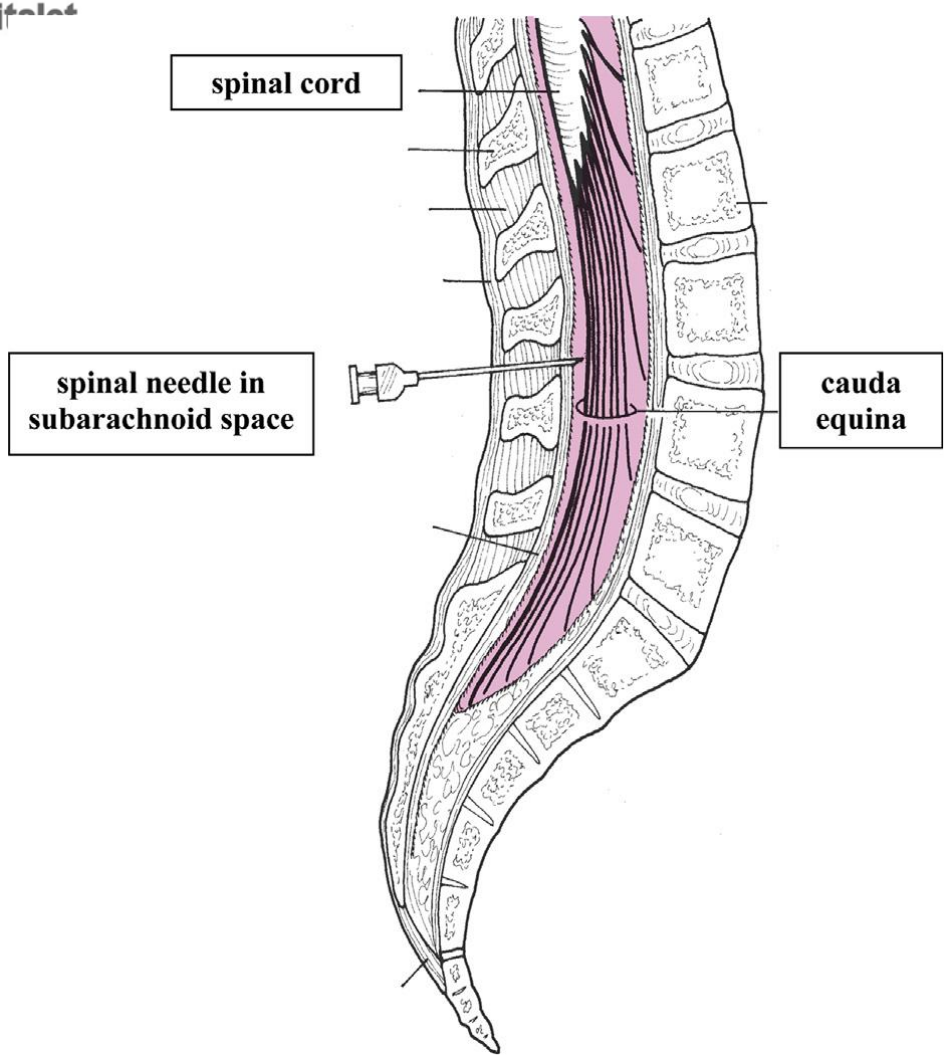
CSF composition

Table 1. Normal Cerebrospinal Fluid Composition

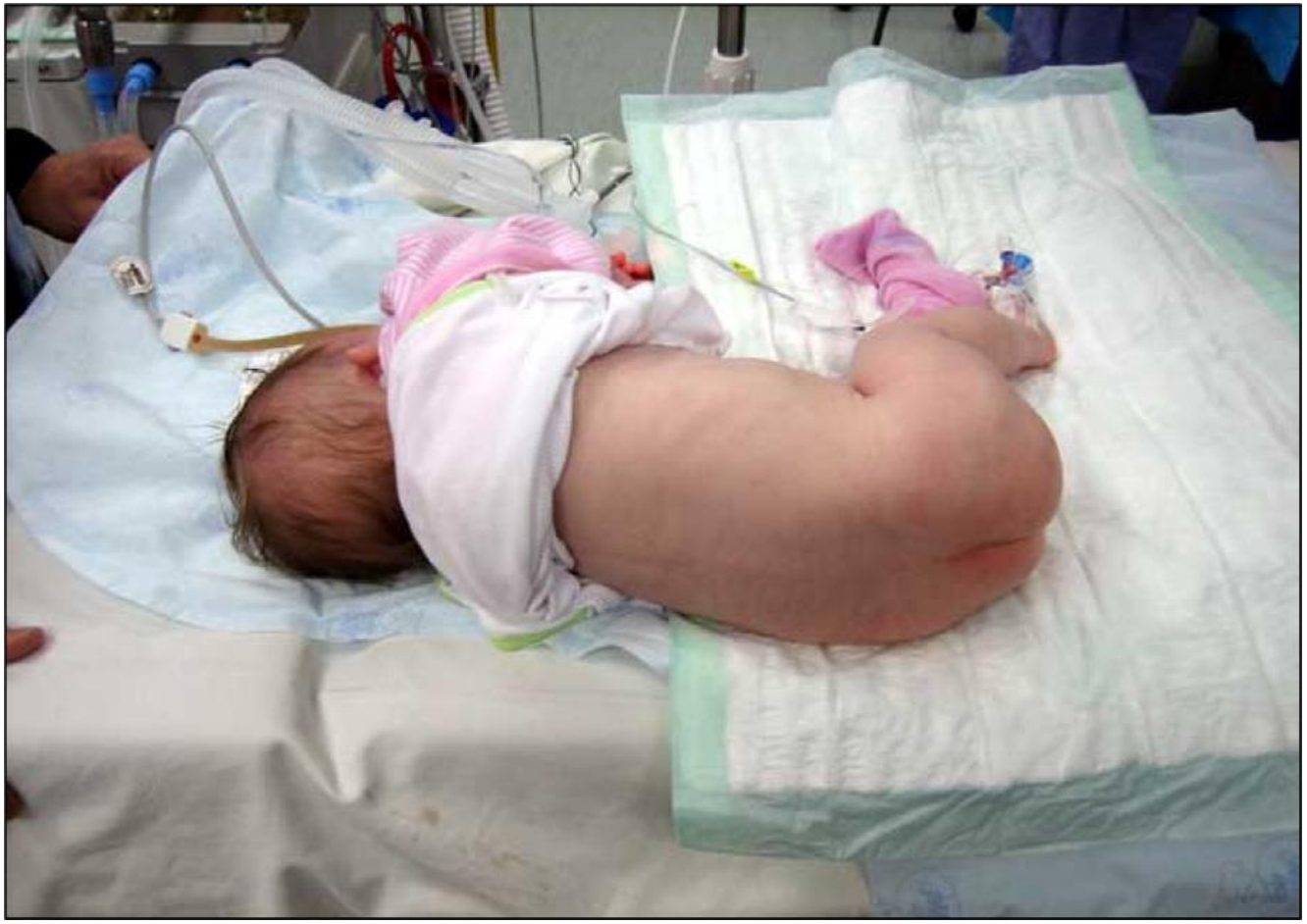
	WBC/mm^3	Glucose (mg/dL)	Protein (mg/dL)
Age	Mean (Range)	Mean (Range)	Mean (Range)
Premature infants	9	50 (24–63)	115 (65–150)
Term newborn	8.2 (0–22)	52 (34–119)	90 (20–170)
0–4 Weeks	11 (0–35)	46 (36–61)	84 (35–189)
4–8 Weeks	7.1 (0–25)	46 (29–62)	59 (19–121)
> 8 Weeks	2.3 (0–5)	61 (45–65)	28 (20–45)

WBC = white blood cells.

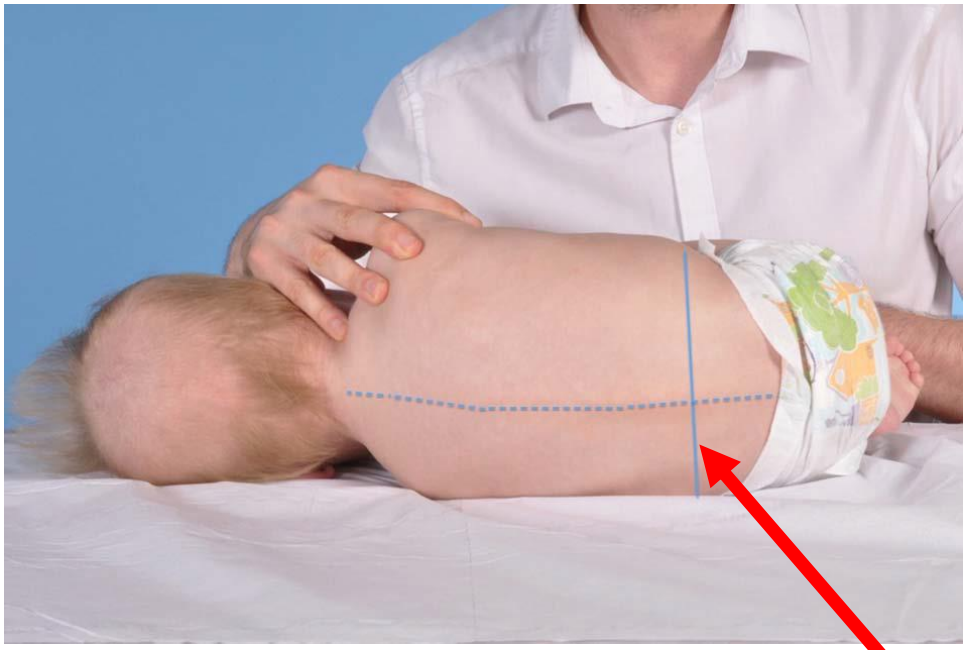
Bonadio 2013



Emergency Medicine Procedures. New York:
McGraw-Hill; 2004:873.

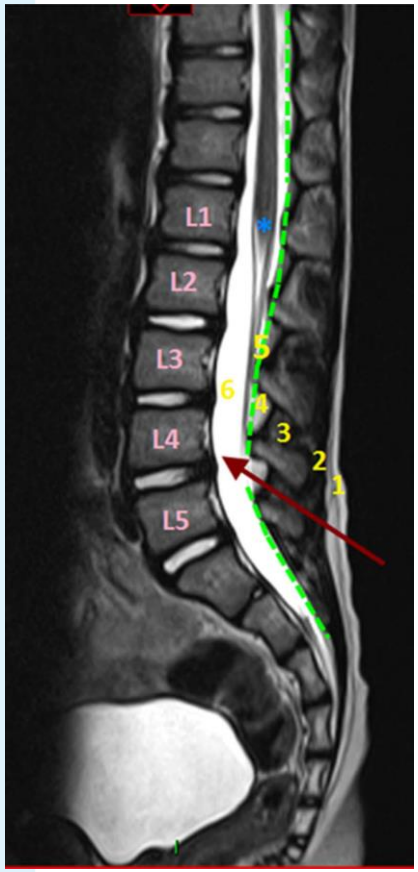


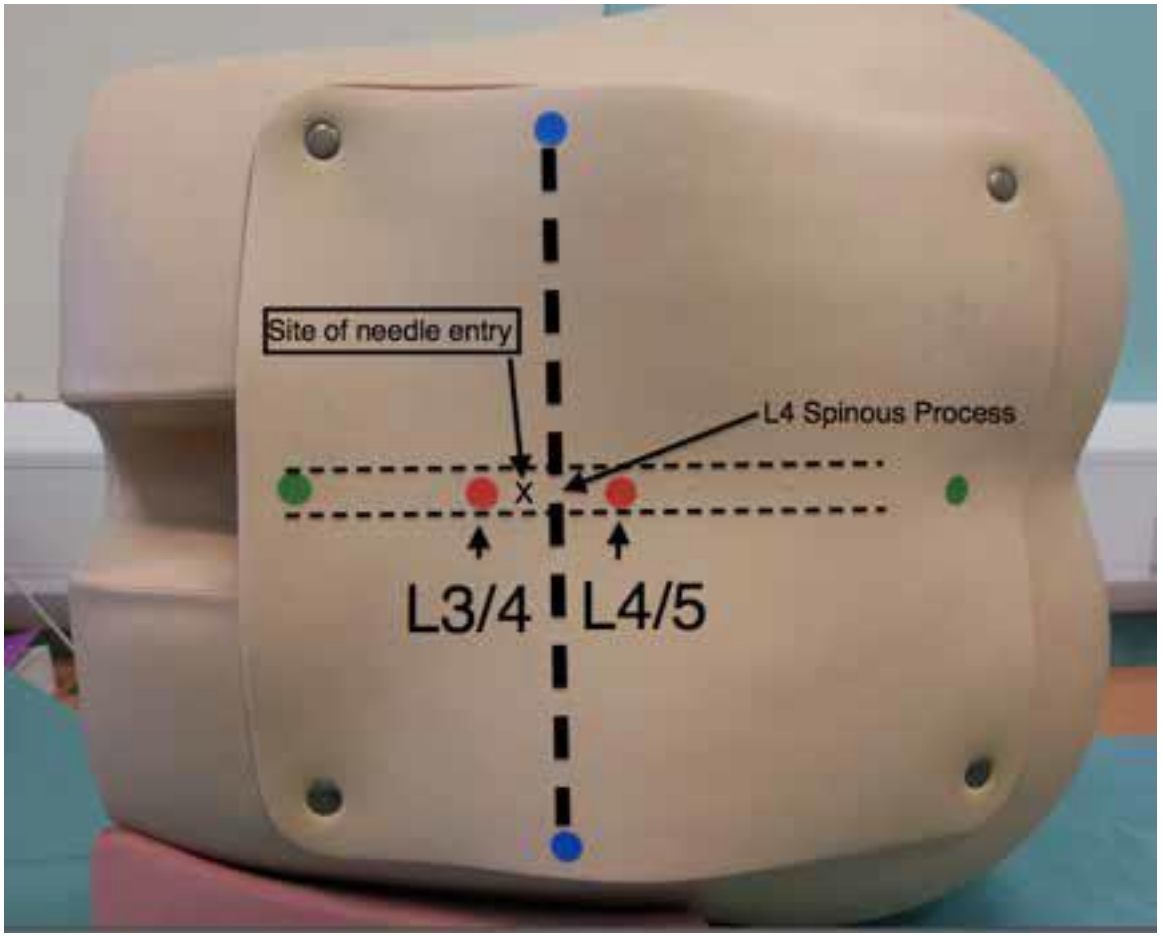
Bonadio 2014



Schulga 2015

Tuffier's line

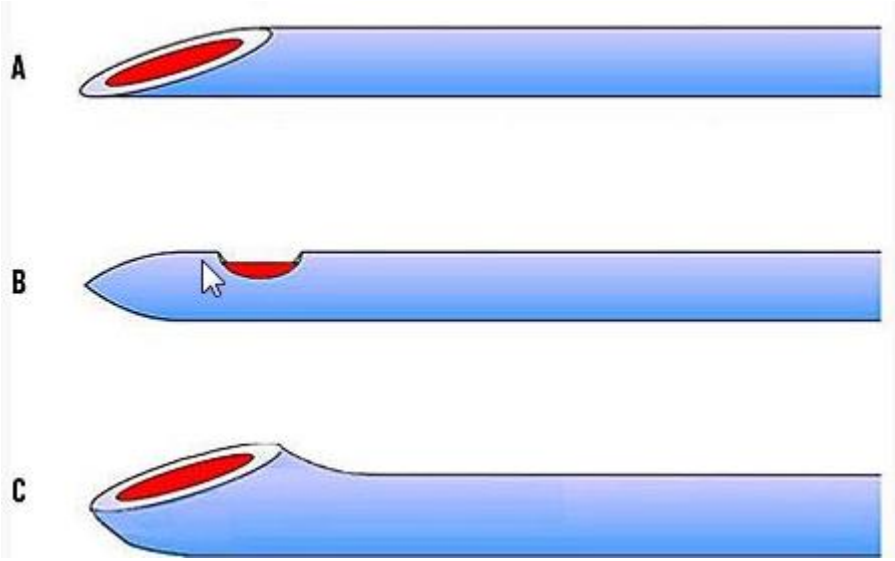




Doherty 2014

Needle type

- PDPH 36% for traumatic 22G Quinck needle
- PDPH 9% for atraumatic 24G needle



Ravn et al 2018

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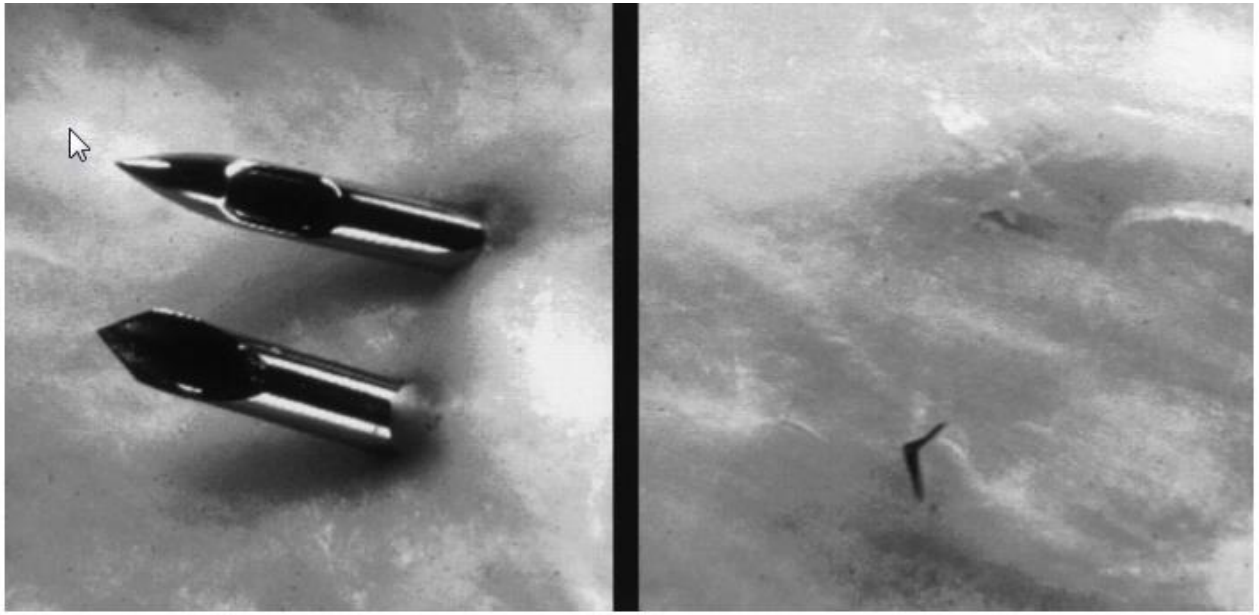
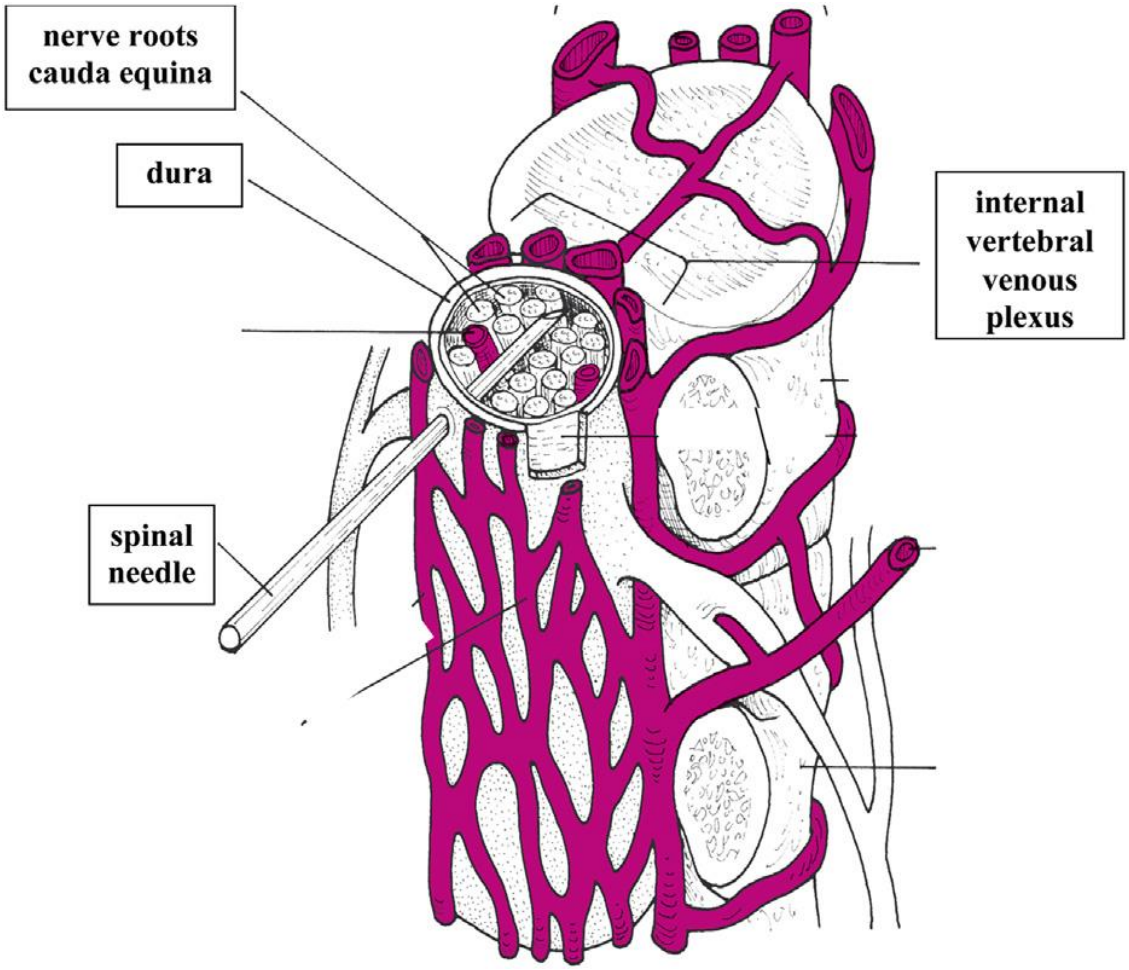
Choice of needle



Strupp et al 2001



Emergency Medicine Procedures. New York: McGraw-Hill; 2004:873.

LP –practical aspects

- depth of LP=0,77cm +(2,56xBSA[m^2])
- Ultrasound guidance possible
- Withdrawl of stilet after perforating dermis may reduce traumatic LP
- Re-insert stilet prior to cannula withdrawl (Strupp 1979)
- Do not aspirate CSF!

Post-dural puncture headache

13-36% after LP. Risc factors:

- Young age
- Female gender
- Previous PDPH
- Staff experience
- Needle type (size and shape)

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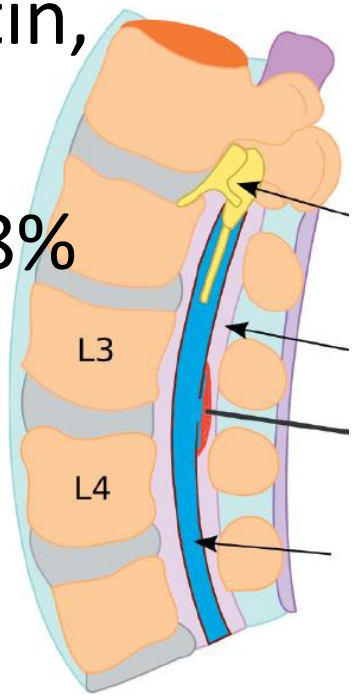
Post-dural puncture headache treatment

- Flat bed rest (little evidence)
- Fluids (little evidence)
- Pharmacological: analgesics, gabapentin, coffeine, aminophylline, steroid
- Epidural blood patch after 2-3 d: 70-98% success rate



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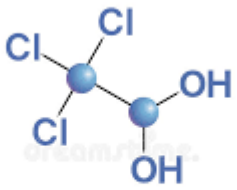
Post-dural puncture headache in children

- Evidence for reduced incidence depending on needle type less clear –no difference between traumatic 22 and 25G needles –Crock 2014
- ? Longer procedure time for smaller needles (22 vs 25G)

Sedation



Chloral hydrate

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Nusinersen

1 year LP experience in Copenhagen

- 7 subject with SMA 1-2, age 0-5 year
- 37 lumbar punctures, 22G Quincke needle

General anæstesia	4
Nitrous oxide	12
Dexmedetomidine	11
Local only	10

- Two operators - 33 in 1. attempt, 4 in 2.or 3. attempt
- One patient admitted for back pain, no postdural headache

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Contraindications

NICE bacterial meningitis guidelines

Box 5 Contraindications to lumbar puncture

- Signs suggesting raised intracranial pressure:
  - Reduced or fluctuating level of consciousness (Glasgow coma scale score <9 or a drop of 3 or more)
  - Relative bradycardia and hypertension
  - Focal neurological signs
  - Abnormal posture or posturing
  - Unequal, dilated, or poorly responsive pupils
  - Papilloedema
  - Abnormal "doll's eye" movements
- Shock (see box 2)
- Extensive or spreading purpura
- The child or young person has recently experienced convulsions and is not yet stabilised
- Coagulation abnormalities:
  - Coagulation results (if obtained) outside the normal range
  - Platelet count below 100×10^9/l
  - Receiving anticoagulants
- Local superficial infection at the lumbar puncture site
- Respiratory insufficiency

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Contraindications

- Signs of raised ICP
- Thrombocytopenia < $40*10^9$/l (relative) or < $20*10^9$/l (absolute) or other coagulation disorders
- Anticoagulation (Vit K antagonists, therapeutic heparin, ADP receptor inhibitors)
- Ongoing seizures/coma/deep sedation
- Cardiovascular instability
- Spinal malformations
- Infection at puncture site

Intrathecal drug admistriation

- Chemotherapy (methotrexate, steroids, cytarabine..)
- Antibiotics (vancomycin)
- Baclofen
- Analgesia –morphine, spinal anaesthesia
- Antisense oligonuceotides for RNA based therapy e.g. nusinersen for SMA
- Gene therapy with viral vectors –SMA, CMT, tumors, neurodegenerative conditions

LP -indications

1. Meningitis/encephalitis
2. Neuroinflammation
3. Neoplasia
4. Metabolic and neurodegenerative conditions
5. Neurosurgery
6. Intrathecal drug administration

Meningitis -Encephalitis

- Assessment of WBC, protein, glucose: *WBC and Protein increased in first two months of life*
- Culture and resistance testing
- IgG ratio
- Antibody titres-ratio to plasma

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Meningitis-Encephalitis

Biofire™ -multiplex PCR

Bacteria	Viruses
Escherichia coli K1	Cytomegalovirus (CMV)
Haemophilus influenzae	Enterovirus
Listeria monocytogenes	Herpes simplex virus 1 (HSV-1)
Neisseria meningitidis	Herpes simplex virus 2 (HSV-2)
Streptococcus agalactiae	Human herpes virus 6 (HHV-6)
Streptococcus pneumoniae	Human parechovirus
Yeast	Varicella zoster virus (VZV)
Cryptococcus neoformans/gattii	

BUT: several 100 pathogens can cause infection!

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Traumatic LP

- Incidence appr. 20% for all children, up to one third in neonates
- Decreased by use of local anaestetic

Correction for traumatic LP

- Not reliably established, BUT
- Appr. 1 WBC/mm3 for every 1000 RC
- Pred WBC= $CSF\ RBC\ \frac{CBC\ WBC}{CBC\ RBC}$
- In adults, 90% of pt. with bacterial meningitis had a ratio of > 10 $\frac{measured\ WBC}{predicted\ WBC}$ but considerable overlap
- Glucose usually unaffected, but protein increased

Autoimmune encephalitis

Only NMDAR and GAD65 have been diagnosed in Denmark (Boesen et al ..)

- GAD65 AB in serum –intrathecal synthesis can be analysed
- NMDA receptor AB (Wang 2015, 43 pt):

➢ 62.8% with + CSF had +serum

➢ 100% patients with +serum had +CSF samples.

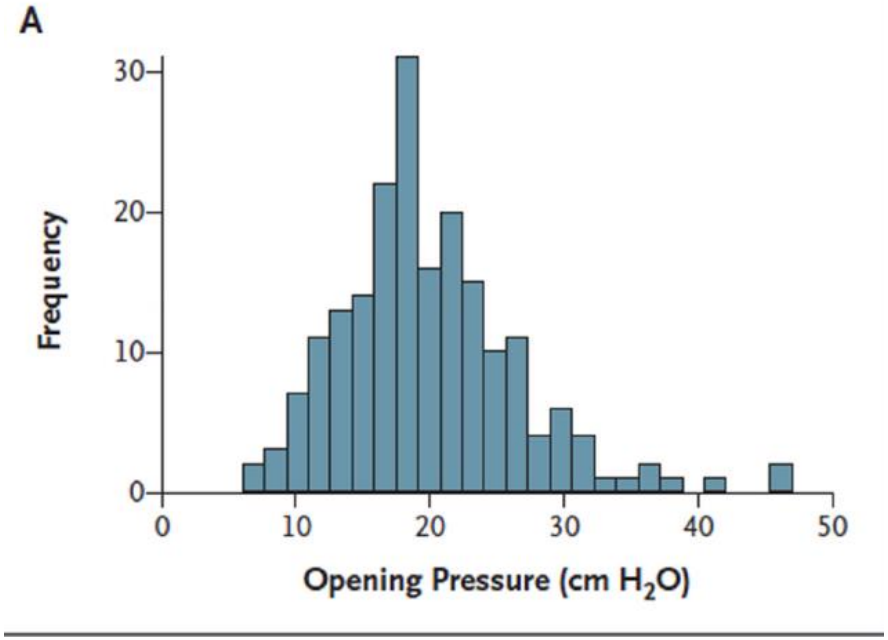
➢ CSF WBC increased in 58%

Demyelination

- Acute demyelination: 63% pleocytosis, 52% pos. oligoclonal bands. OCB only predictive of MS in children older than 12 years (Boesen et al, poster)
- IgG index increased in 80-90% of MS patients, but also in many other conditions –very low specificity

CSV opening pressure in children

- upper limit 28 cm H2O (mean 19,8 ± 6,8)



Avery 2010

CSV opening pressure in children

- Factors influencing opening pressure:

Age?

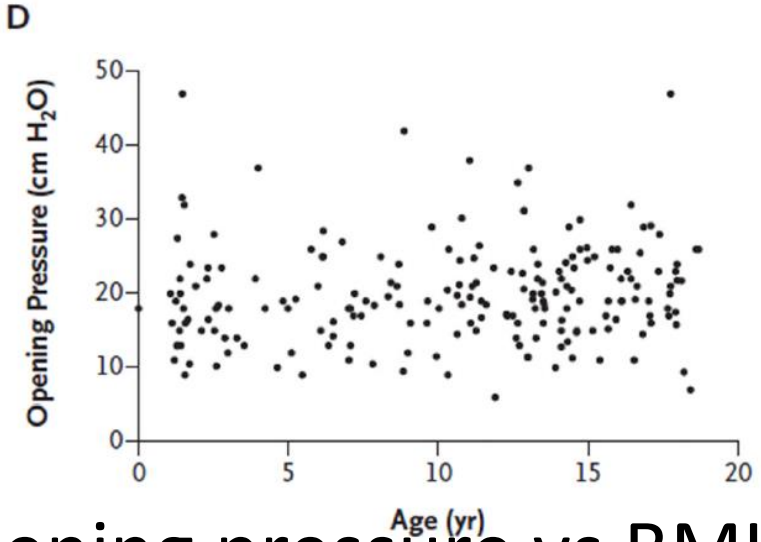
BMI?

Sedation?

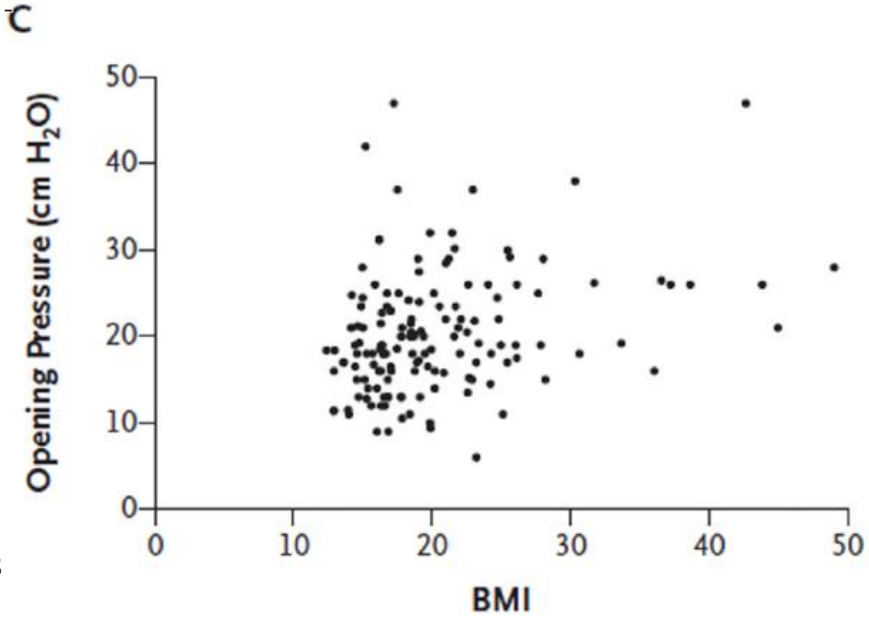
Position?

Avery 2010

Opening pressure vs age



Opening pressure vs BMI -3cm per 10-unit



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Avery 2010

CSV opening pressure in children

- Sedation: depth AND agent
- Children sedated had 3.5cm H2O higher values
- Possible effect of pCO2

Avery 2010

CSV opening pressure in children

No effect of leg position stretched/flexed

Conclusion:

- CSF opening pressure has to be interpreted in a clincal context
- values below 28 cm H2O do not support markedly increased pressure.

CSF pressure

- 90. centile of CSF in 500 children: 28 cm H_2O

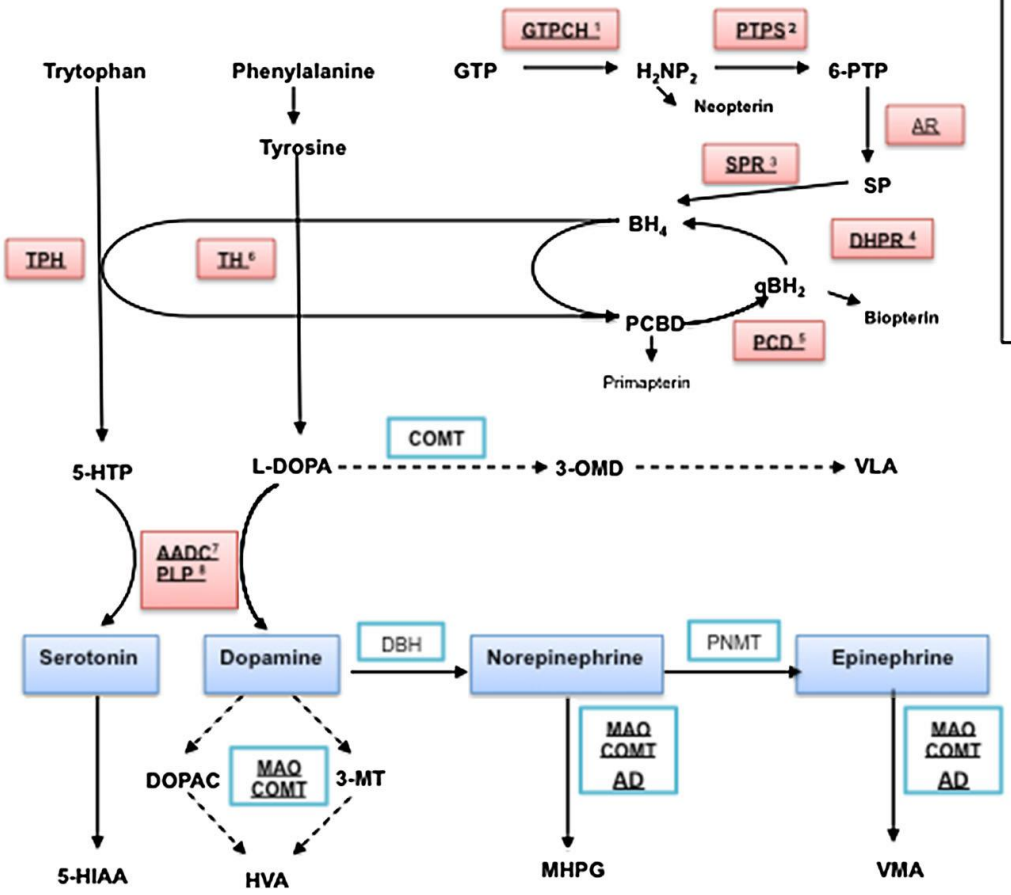
CSF analysis in neurometabolic conditions

- Glucose, lactate
- Amino acids, pipecolic acid
- Dopamin metabolites: HVA, MHPG, VMA
- Serotonin metabolites: 5-MTHF
- Pterins: Biopterin, Neopterin

Neurometabolic conditions

- Mitochondrial disease
- Monoaminergic neurotransmitter disorders
- Disorders of amino acid neurotransmitter metabolism: GABA, glycine, serine
- Disorders of pyridoxine, glucose and folate metabolism

Monoamine neurotransmitter pathway



Sites of neurotransmitter defects:

1. Autosomal dominant and recessive GTPCH deficiency
2. 6 Pyruvoyl-tetrahydrobioterin synthase deficiency (PTPS) deficiency
3. Sepiapterin reductase (SPR) deficiency
4. Dihydropteridine reductase (DHPR) deficiency
5. PCD
6. Tyrosine hydroxylase (TH) deficiency
7. Aromatic L amino acid decarboxylase (AADC) deficiency
8. PLP

Ng, 2014

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TABLE 1.
Selected Cerebrospinal Fluid Abnormalities in Disorders of Monoamine Neurotransmitter Metabolism and Tetrahydrobiopterin Synthesis*

Disorder	Levels in Cerebrospinal Fluid							
	Neopterin	Sepiapterin	Biopterin	5-HTP	HVA	5-HIAA	3-OMD	MHPG
Dopamine beta-hydroxylase deficiency						n	↑	↓↓
Tyrosine hydroxylase deficiency					↓↓	n	n	↓
Aromatic-L-amino acid decarboxylase deficiency				↑↑	↓↓	↓↓	↑↑↑	
Monoamine oxidase A deficiency					↓	↓	n	↓
Dopamine transporter deficiency					↑	n		
Dopamine-serotonin vesicular transport defect					n	n		
Guanosine triphosphate cyclohydrolase deficiency (autosomal recessive)	↓↓		↓↓		↓↓	↓		
6-Pyruvoyl-tetrahydropterin synthase deficiency	↑↑↑		↓↓↓		↓↓	↓↓		
Dihydropteridine reductase deficiency	n		n-↑		↓↓	↓↓		
Pterin-4-α-carbinolamine dehydratase deficiency (Primapterinuria)	↑-↑↑							
Dopa-responsive dystonia (Segawa disease)	↓		↓		↓	↓-n		
Sepiapterin reductase deficiency	n	↑↑	↑		↓↓↓	↓↓↓		

Abbreviations:
5-HIAA = 5-hydroxyindoleacetic acid (derived from serotonin)
5-HTP = 5-hydroxytryptophan
HVA = Homovanillic acid (derived from dopamine)
3-OMD = 3-ortho-methyldopa (derived from L-DOPA)
MHPG = 3-methoxy-4-hydroxyphenylglycol (norepinephrine metabolite)

Rodan 2015, adapted from Hoffman, 2014

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Mercimek-Mahmutoglu *et al. Orphanet Journal of Rare Diseases* (2015) 10:12
DOI 10.1186/s13023-015-0234-9

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Prevalence of inherited neurotransmitter disorders in patients with movement disorders and epilepsy: a retrospective cohort study

Saadet Mercimek-Mahmutoglu[1,2,6*], Sarah Sidky[1], Keith Hyland[3], Jaina Patel[1], Elizabeth J Donner[4], William Logan[4], Roberto Mendoza-Londono[1], Mahendranath Moharir[4], Julian Raiman[1], Andreas Schulze[1,2], Komudi Siriwardena[1], Grace Yoon[1,4] and Lianna Kyriakopoulou[5]

Abstract

Background: Inherited neurotransmitter disorders are primary defects of neurotransmitter metabolism. The main

154 patiens from Hospital
for Sick Children, Toronto

-epilepsy and movement disorder

6 patients with inherited neurotranmitter disorders
14 patients with non-neurotransmitter disorders
130 patients without diagnosis

The Turkish Journal of Pediatrics 2012; 54: 52-58 *Original*

When do we need to perform a diagnostic lumbar puncture for neurometabolic diseases? Positive yield and retrospective analysis from a tertiary center

Göknur Haliloğlu[1], Emine Vezir[1], Leyla Baydar[2], Saniye Önol[2], Serap Sivri[2], Turgay Coşkun[2], Meral Topçu[1]

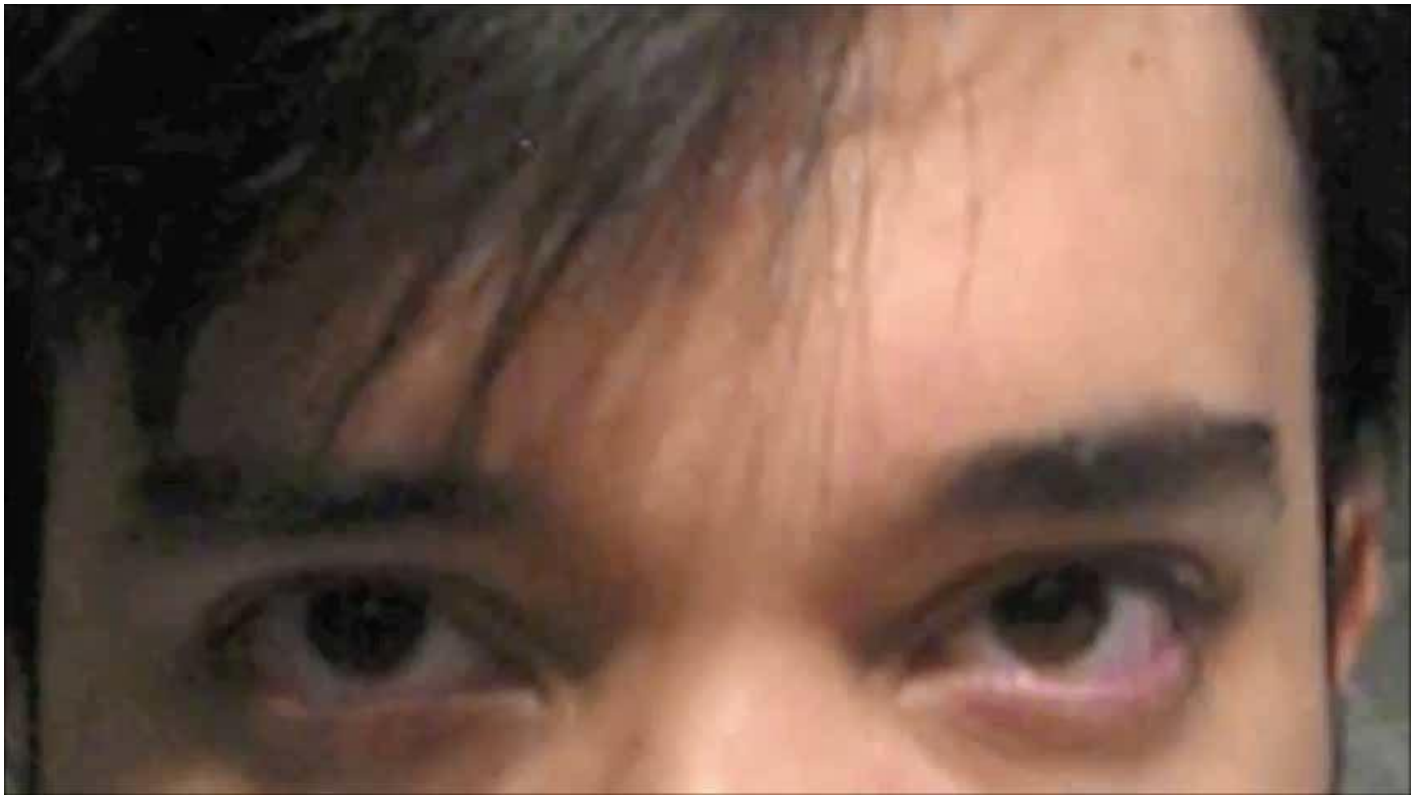
Units of [1]Pediatric Neurology, and [2]Metabolism and Nutrition, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Haliloğlu G, Vezir E, Baydar L, Önol S, Sivri S, Coşkun T, Topçu M. When do we need to perform a diagnostic lumbar puncture for

When to do LP for neurometabolic disease?

- Haliloglu 2012: 62 pt, positive yield 16/62 (25,8%).
- Significant: diurnal variation, oculogyric crisis and consanguinity

Oculogyric crisis



Solberg 2017

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When to do LP for neurometabolic disease?

- Infantile (epileptic) encephalopathy
- Microcephaly?
- Unexplained movement disorders:
  parkinsonism, dystonia and ataxia, hypotonia, hypertonia, hypokinesia especially with fluctuating symptoms
- Dysautonomia, sleep disturbance
- Ptosis, eye movement disorders
- Progressive motor or cognitive symptoms

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2y 1m old boy

- First child of consanguineous parents originally from Pakistan
- Developmental arrest since 8 months, seizures since 6 months, intitially rare. Hypotonia, failure to thrive
- Daily seizures with: downward eye deviation, stiffness of one or both sides, oral dyskinesia, lasting hours

(cont.)

- CSF analysis 2 y 5 m old: ↓↓↓ HVA, normal 5 HIAA
- Homozygeous for mutation in exon 9 tyroxin hydroxylase (TH) gene
- Diagnosis: **TH-Deficient Infantile Parkinsonism with Motor Delay**
- Treatment with levodopa and later seligiline (MAO B inhibitor)

CSF sampling for metabolic disease:

- 4 hours glucose fasting
- Know your normal values: craniocaudal gradient of neurotransmitters
- Glucose, lactate, aminoacids, neurotransmitters
- Spin immediately if blood contaminated (lab technician present!)
- Snap freeze in liquid nitrogen immediately after