Gyermekneurológiai - epileptológiai aktualitások

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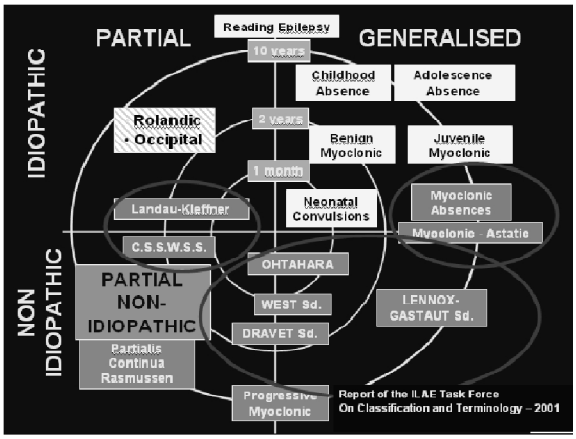
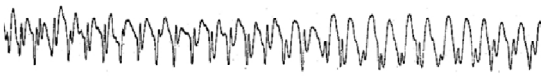
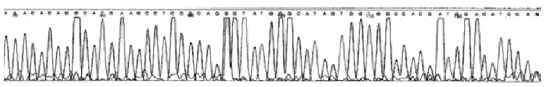


epileptológiai diagnosztika

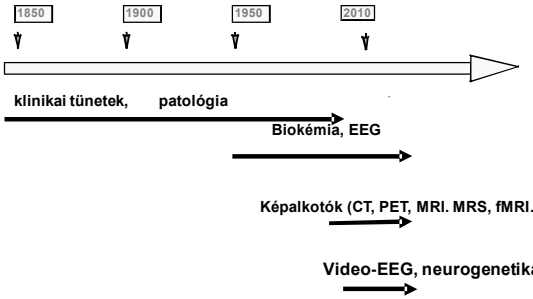
Epilepsy 1936

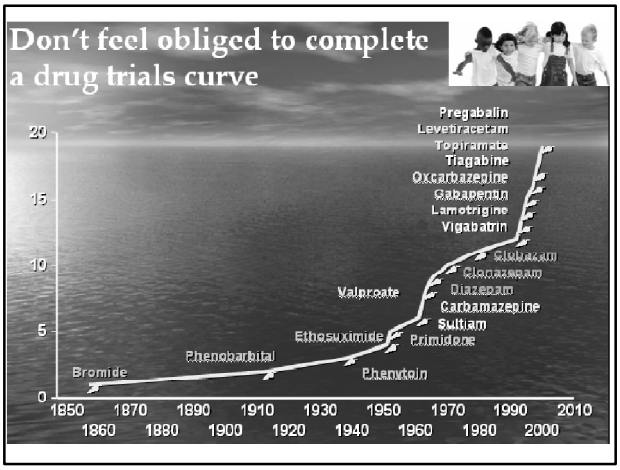


Epilepsy 2020?



Diagnosztikus eszközök a gyermek epileptológiai diagnosztikában





Molecular targets of antiepileptic drugs

Drug	Na^+ channel	Ca^{2+} channel	GABA system	Glutamate system	Other major targets
Phenytoin	I_{Nat} I_{NaP}	HVA			
Carbamazepine	I_{Nat}	HVA			
Oxcarbazepine	I_{Nat}	HVA			
Lamotrigine	I_{Nat}	HVA			
Zonisamide	I_{Nat}	T-type			
Valproate	I_{Nat}? I_{NaP}	T-type?	GAD↑, turnover↑	NMDA	
Felbamate	I_{Nat}	HVA	$GABA_AR$	NMDA	
Topiramate	I_{Nat} I_{NAP}	HVA	$GABA_AR$	KA/AMPA	
Ethosuximide	I_{NAP}?	T-type			
Phenobarbital		HVA	**$GABA_AR$**	KA/AMPA	
Gabapentin		HVA (α2δ)	GAD↑, turnover↑		
Pregabalin		HVA (α2δ)	GAD↑		
Levetiracetam		HVA	?		SV2a
Benzodiazepines			$GABA_AR$		
Vigabatrin			GABA-T↓		
Tiagabine			Uptake↓		

- Levetiracetam
- Lacosamide
- Brivaracetam
- Padsevonil

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Pregabalin as Adjunctive Treatment for Focal Onset Seizures in Pediatric Patients: A Randomized Controlled Trial

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Abstract

Efficacy and safety of pregabalin as adjunctive treatment for children (aged 4–16 years) with partial-onset seizures, hereafter termed focal onset seizures for this study, was evaluated. This double-blind, randomized, placebo-controlled, international study had 3 phases: 8-week baseline, 12-week double-blind treatment (2-week dose escalation; 10-week fixed dose), and 1-week taper. Selection criteria included experiencing focal onset seizures and receiving a stable regimen of 1 to 3 antiepileptic drugs. Study treatments were pregabalin 2.5 mg/kg/d, 10 mg/kg/d, or placebo; doses were increased to 3.5 or 14 mg/kg/d for subjects weighing <30 kg. The key endpoints were change in $\log_e$(28-day seizure rate), achieving a ≥50% seizure responder rate, safety, and tolerability during double-blind treatment. Subjects (n = 295; mean age 10.2 years, 55% male, 69% white) were randomized to pregabalin 2.5 mg/kg/d (n = 104), 10 mg/kg/d (n = 97), or placebo (n = 94). A statistically significant reduction in $\log_e$(28-day seizure rate) was demonstrated with pregabalin 10 mg/kg/d (a 19.9% improvement over placebo; $P = .0185$). Seizure frequency was numerically improved (statistically nonsignificant) with pregabalin 2.5 mg/kg/d ($P = .2577$). Responder rate significantly favored pregabalin 10 mg/kg/d (40.6%, $P = .0068$) compared with placebo (22.6%) and was numerically improved with pregabalin 2.5 mg/kg/d (29.1%, $P = .2600$). Common adverse events (≥10% of any group) in 10 mg/kg/d, 2.5 mg/kg/d, and placebo groups, respectively, included somnolence (35.8%, 17.3%, 13.8%), increased weight (13.4%, 3.8%, 4.3%), and increased appetite (10.3%, 6.7%, 4.3%). Pregabalin 10 mg/kg/d demonstrated efficacy in seizure frequency reduction in children with focal onset seizures compared with placebo, and both pregabalin doses were generally safe and well tolerated.

www.clinicaltrials.gov identifier NCT01389596; EudraCT #2010-020852-79

Keywords
pregabalin, focal onset seizures, children, pediatric

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ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Efficacy and tolerability of adjunctive lacosamide in pediatric patients with focal seizures

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Neurology® 2018;91:e1713–e1726. doi:10.1212/WNL.0000000000006376

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Criteria for rating therapeutic and diagnostic studies
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Abstract

Objective
To evaluate efficacy and tolerability of adjunctive lacosamide in children and adolescents with uncontrolled focal (partial-onset) seizures.

Methods
In this double-blind trial (SP0969; NCT01921205), patients (age ≥4–<17 years) with uncontrolled focal seizures were randomized (1:1) to adjunctive lacosamide/placebo. After a 6-week titration, patients who reached the target dose range for their weight (<30 kg: 8–12 mg/kg/d oral solution; ≥30–<50 kg: 6–8 mg/kg/d oral solution; ≥50 kg: 300–400 mg/d tablets) entered a 10-week maintenance period. The primary outcome was change in focal seizure frequency per 28 days from baseline to maintenance.

Results
Three hundred forty-three patients were randomized; 306 (lacosamide 152 of 171 [88.9%]; placebo 154 of 172 [89.5%]) completed treatment (titration and maintenance). Adverse events (AEs) were the most common reasons for discontinuation during treatment (lacosamide 4.1%; placebo 5.8%). From baseline to maintenance, percent reduction in focal seizure frequency per 28 days for lacosamide (n = 170) vs placebo (n = 168) was 31.7% ($p = 0.0003$). During maintenance, median percent reduction in focal seizure frequency per 28 days was 31.7% for lacosamide and 21.7% for placebo. Fifty percent responder rates (≥50% reduction) were 52.9% and 33.3% (odds ratio 2.17, $p = 0.0006$). During treatment, treatment-emergent AEs were reported by 67.8% lacosamide-treated patients (placebo 58.1%), most commonly (≥10%) somnolence (14.0%, placebo 5.2%) and dizziness (10.5%, placebo 3.5%).

Conclusions
Adjunctive lacosamide was efficacious in reducing seizure frequency and generally well tolerated in patients (age ≥4–<17 years) with focal seizures.

ClinicalTrials.gov identifier:

Lacosamide

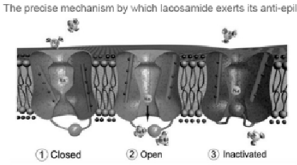
MOA: Enhancement of sodium channel slow inactivation

Lacosamide selectively affects sodium channel slow inactivation but not fast inactivation like all other sodium channel blocking AEDs

Enhancement of slow inactivation reduces the long-term availability of sodium channels

- **reduction of pathological hyperexcitability** while leaving physiological activity intact
- Lacosamide selectively blocks the electrical activity of neurons that are chronically depolarized compared with those at more normal resting potentials

The precise mechanism by which lacosamide exerts its anti-epileptic effects in humans remains to be fully elucidated



Beyreuther et al. CNS Drug Rev 2007;13(1):21–42.
Brandt et al. Epilepsia 2006;47(11):1803–9.
Wang et al. J Biol Chem 2010 ; 285 (33): 25296–307.

Brivaracetam

- After identification of **SV2A** as the **primary MOA of LEV**, the development program was **targeted at discovering** other molecules with **pharmacological activity at the binding site**.
- **Function of SV2A is not fully established** - known to be implicated in modulation of synaptic vesicle exocytosis and neurotransmitter release.
- **SV2A modulates** the pool of **readily available vesicles for exocytosis**.
- **Correlation between ligand affinity and anticonvulsant potency** in focal (partial-onset) seizures.

Affinity and selectivity for SV2A of BRV and LEV[1]

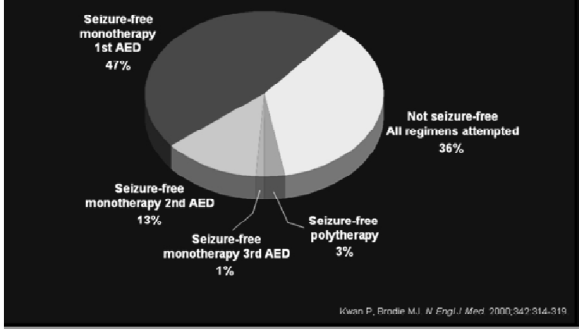
Property	BRV	LEV
SV2A affinity Human cortex; Ki (μM)	0.05 μM	1.6 μM
HVA Ca^{2+} channel current IC_{50} value (μM)	Inactive up to 1000 μM	13.9 μM
AMPA gated current IC_{50} value (μM)	Inactive up to 100 μM	268 μM

BRV has a higher affinity and selectivity for SV2A than LEV*

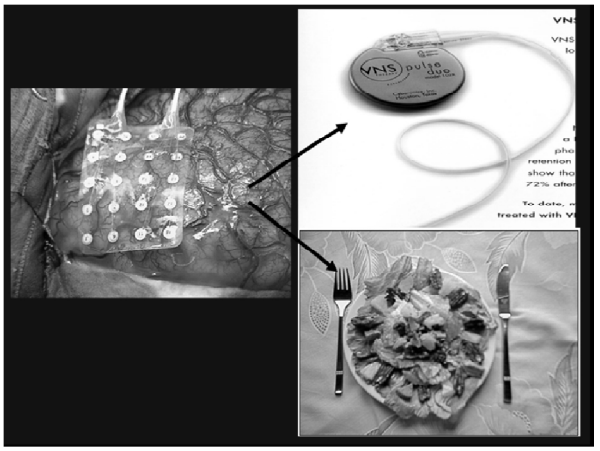
*Unknown clinical relevance

1. Adapted from D'Souza J & Perucca E. 'Brivaracetam' in Shorvon S, Perucca E, Engel J (Eds.) The Treatment of Epilepsy. 2016. John Wiley & Sons, Ltd. pp 420–424.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BRV, brivaracetam; IC_{50}, inhibitory half-maximal concentration; Ki, equilibrium constant; LEV, levetiracetam; MOA, mechanism of action; SV2A, synaptic vesicle protein 2A.

AE algoritmusok: **Rohammentességi ráta**

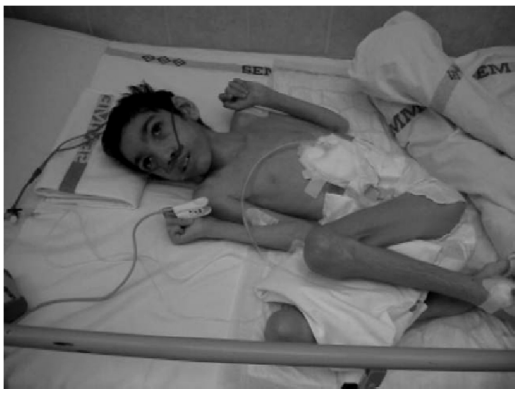


Kwan P, Brodie M.J. *N Engl J Med* 2000;342:314–319.



Korai kezdetü epilepszia és Terápia rezisztencia esetén:

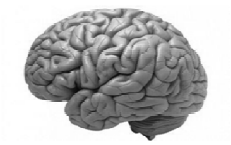
- Epilepsziás encephalopathia ??
- Korrekt-e diagnózisunk?
- Korrekt-e a terápiaválasztásunk?
- Time is brain !!!

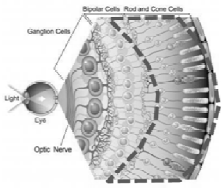


Neurális Ceroid Lipofuscinosis (NCL)

Lysomális tárolási betegség csoport

BRAIN and **RETINA**





Neurális Ceroid Lipofuscinosis (NCL)

PME: **p**rogressziv **m**yoklonus **e**pilepszia

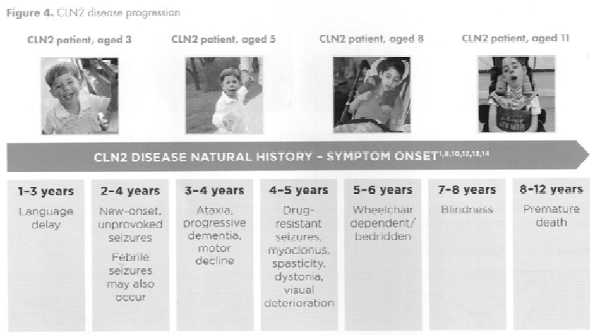
Familiaris amaurotikus idiotia

Spielmeyer -Vogt – Batten betegség
Kuf betegség

Neurális Ceroid Lipofuscinosis (NCL)

Klinikai kép: triad

- Epilepsziás rohamok
- Rapidan kifejlődő dementia
- vakság



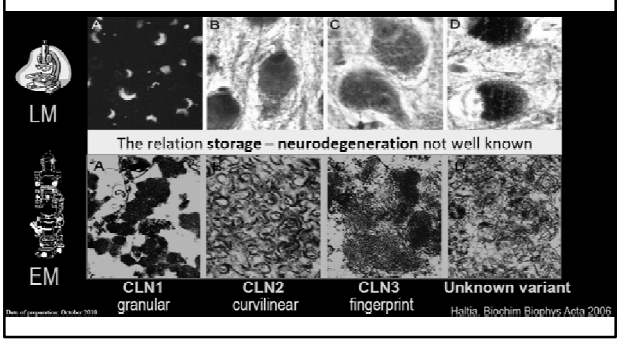
NCL: genetikai és életkori manifesztáció

	CLN1 Disease	infantile	late infantile	juvenile	adult
Most frequent	CLN2 Disease		late infantile	juvenile	
Most frequent	CLN3 Disease			juvenile	
	CLN4 Disease				adult, Kufs autos. dominant
	CLN5 Disease		late infantile	juvenile	adult
	CLN6 Disease		late infantile		adult, Kufs A
	CLN7 Disease		late infantile		
	CLN8 Disease		late infantile	juvenile	
	CLN10 Disease	congenital		juvenile	adult
	CLN11 Disease				adult
	CLN12 Disease			juvenile	
	CLN13 Disease				adult, Kufs B
	CLN14 Disease	infantile			

NCL: genetikai és életkori manifesztáció

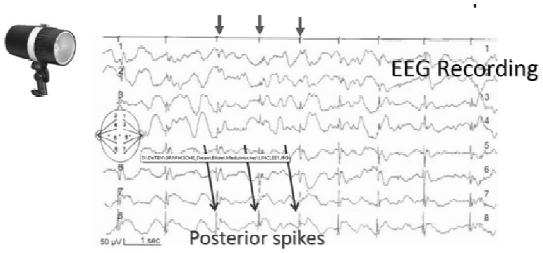
Deficiencies	*Gene symbol*	*(Alternatives)*	*Protein*
Soluble lysosomal enzymes	*CLN1*		Palmityl protein thioesterase 1
	CLN2		Tripeptidyl peptidase 1 (TPP1)
	CLN10	*(CTSD)*	Cathepsin D
	CLN13	*(CTSF)*	Cathepsin F
Nonenzyme proteins	*CLN3*		Lysosomal membrane protein
	CLN4	*(DNAJC5)*	Soluble cysteine string protein α
	CLN5		Soluble lysosomal protein
	CLN6		Transmembrane protein
	CLN7	*(MFSD8)*	Transmembrane protein
	CLN8		Transmembrane protein
	CLN11	*(GRN)*	Progranulin
	CLN14	*(KCD7)*	Potassium channel protein
Other enzymes	*CLN12*	*(ATP13A2)*	ATPase

Ceroid lipofuscin felhalmozódás

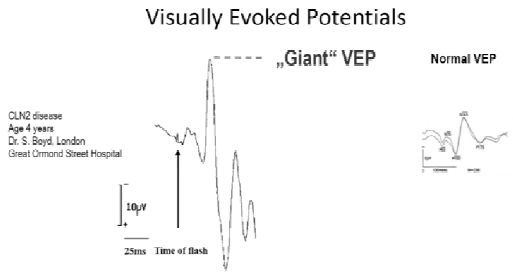


CNL2 betegség: késő csecsemőkori forma

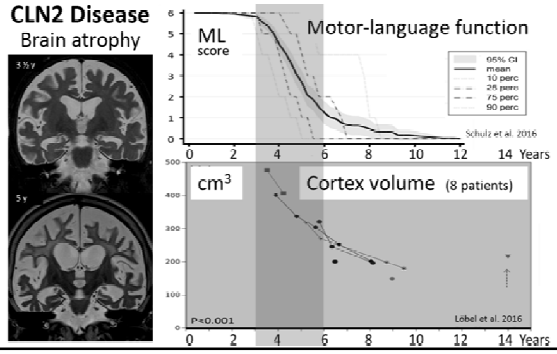
Alacsony frekvenciáju fényingerléskor: spike aktivitás a hátsó regiókban



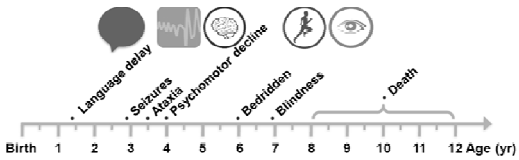
CNL2: késő csecsemőkori



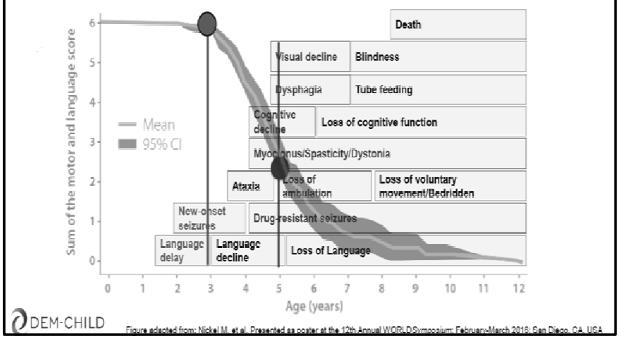
CNL2 betegség: késő csecsemőkori forma



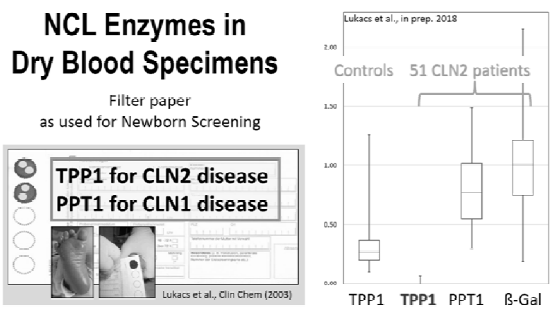
NCL2: tünettan



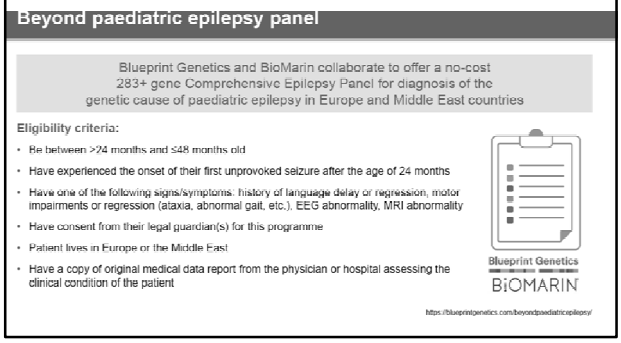
Korai kezdetű gyermekkori epilepsziákban a CNL2 betegségre gondolnunk kell !!



NCL2 diagnosztika: vércsepp



NCL2: genetikai dioagnosztika



NCL2 diagnosztika (USA)

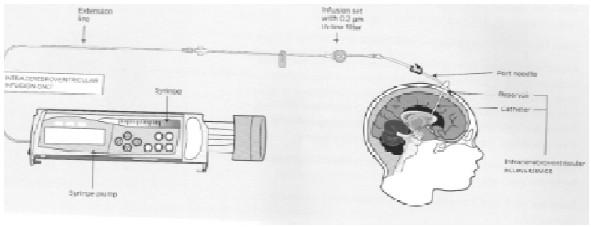
Early-Life Epilepsies and the Emerging Role of Genetic Testing.
Berg AT et al. JAMA Pediatr. 2017 Sep 1;171(9):863-871

For metabolic disorders, we plan to offer neonatal metabolic genetic screening for newborns.
Before disease onset

All patients with early-life epilepsies should have genetic testing incorporated into the initial evaluation when clinical diagnosis is made.
At seizure onset

Detection of Infantile Batten Disease by Tandem Mass Spectrometry Assay of PPT1 Enzyme Activity in Dried Blood Spots.

Enzimpótló kezelés



NCL: Take home message

Historic clinical hallmark is the combination of

Dementia

Visual loss due to retinopathy

Epilepsy

NCL: a gyermekkori dementia leggyakoribb oka

Glükóz-transzporter-1 defektus szindróma
(GLUT1 DS) a *metabolikus encephalopathiák egyike*

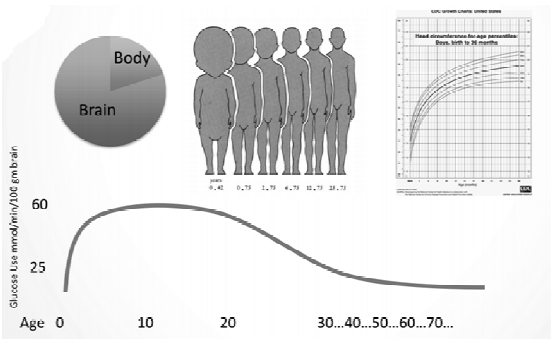
N Engl J Med (1991):

szinonímák:

- **De Vivo szindróma**

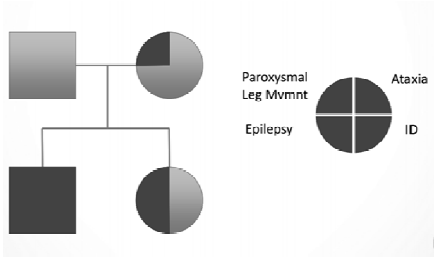
- Encephalopathy due to GLUT1 deficiency
- Glucose transport defect, blood-brain barrier
- Glucose transporter protein syndrome

a **<u>gyermekkori agy</u>** energia ellátása:
a gyermekkori agy **<u>nagyon „önző”</u>**

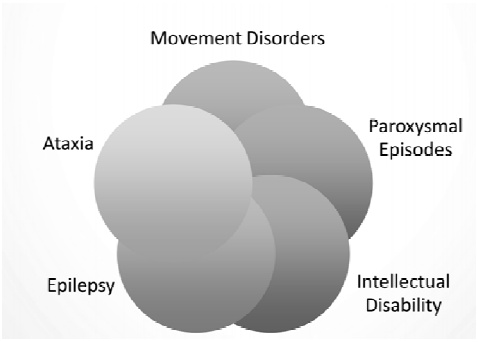


GLUT1DS: klinikai tünetek

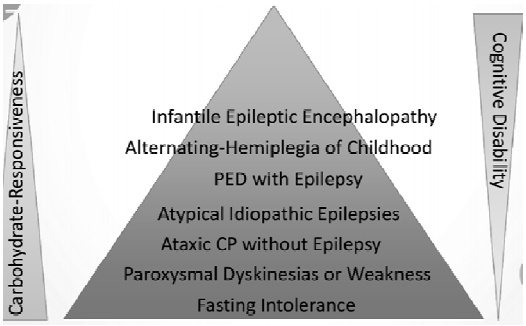
egy családon belül, ugyanazon gén mutáció esetén változatosak a klinikai tünetek



GLUT1DS: Fenotipus spektrum



GLUT1DS: tünettan – spektruma



Glükóz transporter 1: GLUTI

- **SLC2AI** **Mutációk**:
  Solute **c**arrier familiy **2**, member **1**

- Komplex Phenotípus: *legismertebb a*

GLUT1·deficiens encephalopathia

aut. dominans metabolikus encephalopathia
- microcephalia
- infantilis korban kezdödö refrakter görcsök
- kognitiv károsodás
- complex motoros fejlödési zavarok

GLUT1DS: Epilepszia

Intractábilis epilepszia:
kezdet: < 3 éves életkor
rohamforma: absence ill. myoklonusok

Pong és mtsai 87 GLUT1DS beteg közül 78 esetében (90%) volt jelen epilepszia az átlagos betegség kezdet 8 hónapos életkor volt
- többféle rohaforma:
  - generalizált tónusos-klónusos roham (53%)
  - **absence** (49%)
  - komplex parciális roham (37%)
  - **myoklónusos roham** (27%)
  - atóniás roham (26%)
  - tónusos roham (12%)
  - simpla parciális roham (3%)
  - infantilis spasmus (3%)

1. De Giorgis V, Veggiotti P. "GLUT1 deficiency syndrome 2013: Current state of the art" Seizure 22 (2013) 803–811
2. Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcome. Epilepsia 2012;53(9):1609–10.

Diagnózis: **Genetikai teszt**

DE:
- **SLC2A1 mutáció, duplikáció vagy deléció** a betegek ~ 70 – 80 %-nál igazolható
- Gén diagnosztikai világszerte hozzáférhető
- a negatív genetikai teszt nem zárja ki a GLUT1DS fennállását
- nem ismerjük mindazon géneket melyek segítenek abban, hogy a sejtmebránban a GLUT1 transzporter megfelelő helyre kerüljön, müködjön
- a terápiát nem befolyásolja, hogy a genetikai eltérés fennállása igazolható-e vagy nem

GLUT1D: Diagnózis

normális vércukorszint mellett

↓

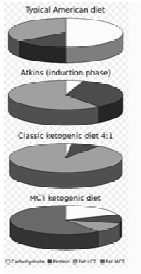
liquor glükóz: <2,5 mmol/l (éhezési)

DIAGNOSZTIKUS ÉRTÉKŰ!

- **liquor / vér glükóz kvóciens: <0,5**

GLUT1D Terápia:

Ketogén diéta: korai kezdettel !!!



központi idegrendszer alternatív energia ellátása ketózis útján

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