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KLINIKA DĚTSKÉ
NEUROLOGIE

Cílená terapie epilepsií podmíněných patogenními variantami v genu *KCNQ2*

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KCNQ2-Related Disorders

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KCNQ2-Related Disorders: Included Phenotypes¹

More common presentations

- Self-limited familial neonatal epilepsy (SLFNE)
- Neonatal-onset developmental and epileptic encephalopathy (NEO-DEE)

Less common presentations

- Neonatal encephalopathy with non-epileptic myoclonus
- Non-neonatal-onset developmental and epileptic encephalopathy
- Isolated intellectual disability

Table 4. Treatment of Manifestations in Individuals with a KCNQ2-Related Disorder

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Education of parents/caregivers¹ • Seizures in persons w/SLFNE are generally controlled w/conventional ASM treatment, while seizures in persons w/NEO-DEE may be resistant to multiple ASMs alone or in combination. • Per a recent systematic review on ASM treatment in KCNQ2-related disorders,² 40/133 persons (~30%) w/the SLFNE phenotype experienced seizure freedom spontaneously; phenobarbital & sodium channel blockers (CBZ, OXC, LTG, & PHT) most often → seizure freedom in the remainder.³ • In persons w/KCNQ2-NEO-DEE, seizure freedom was more likely to be achieved when on sodium channel blockers.⁴

Rapid and safe response to low-dose carbamazepine in neonatal epilepsy

Sands et al., 2016



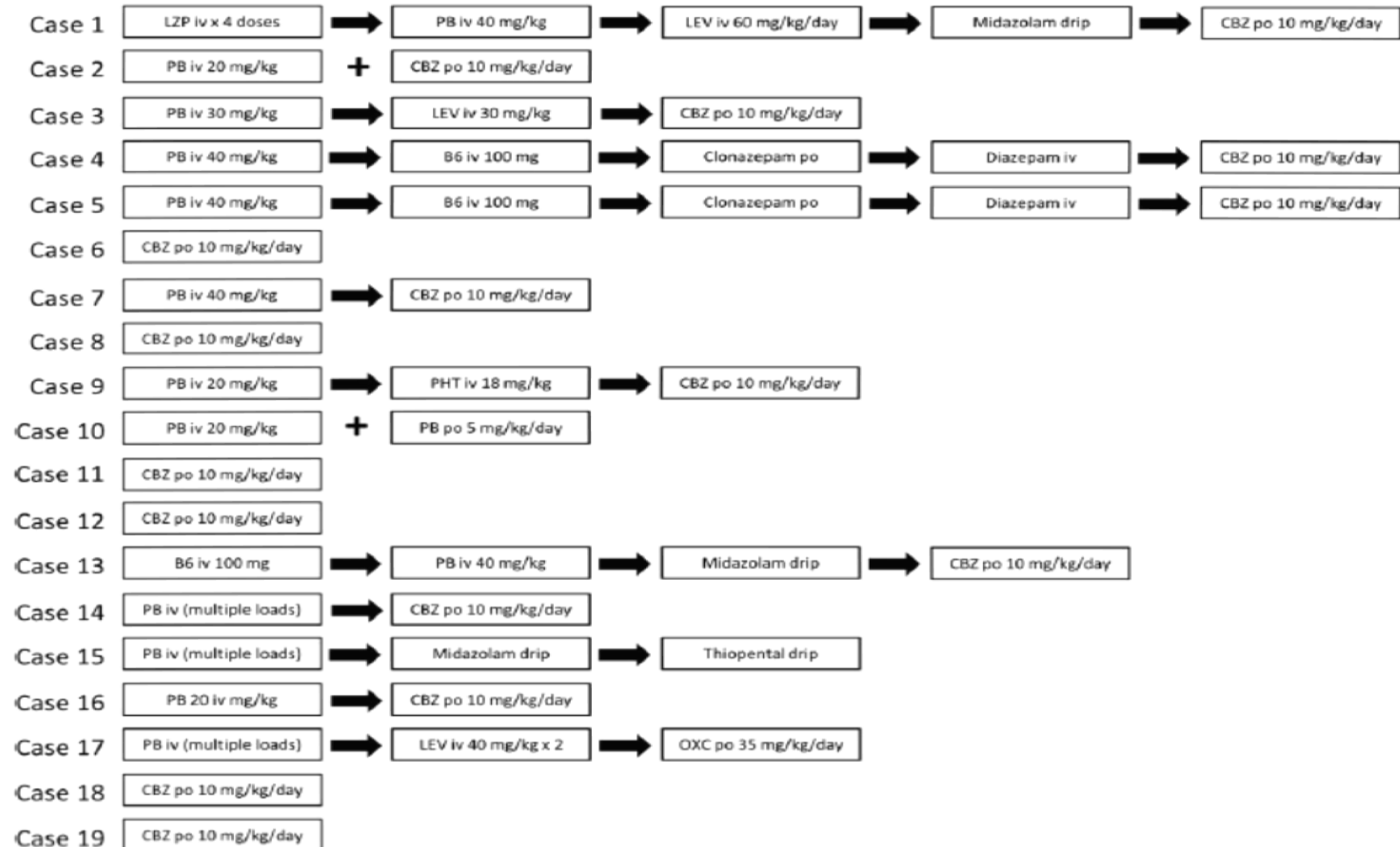
- u 16 z 19 dětí familiární benigní neonatální křeče

- u 16 z 19 dětí *KCNQ2* či *KCNQ3* mutace

- 14 dětí s mutací bylo bez záchvatů do několika hodin po podání nízké dávky CBZ či oxCBZ

- u 3 dětí bez mutace pozitivní efekt CBZ

Treatment responses in BFNE



SL(F)NE - benigní (familiární) neonatální epilepsie



- patogenní varianty v *KCNQ2* - funkčně LoF o 30-40%
- spontánní ústup ve 30%
- terapie u ostatních:
 - PB nebo CBZ

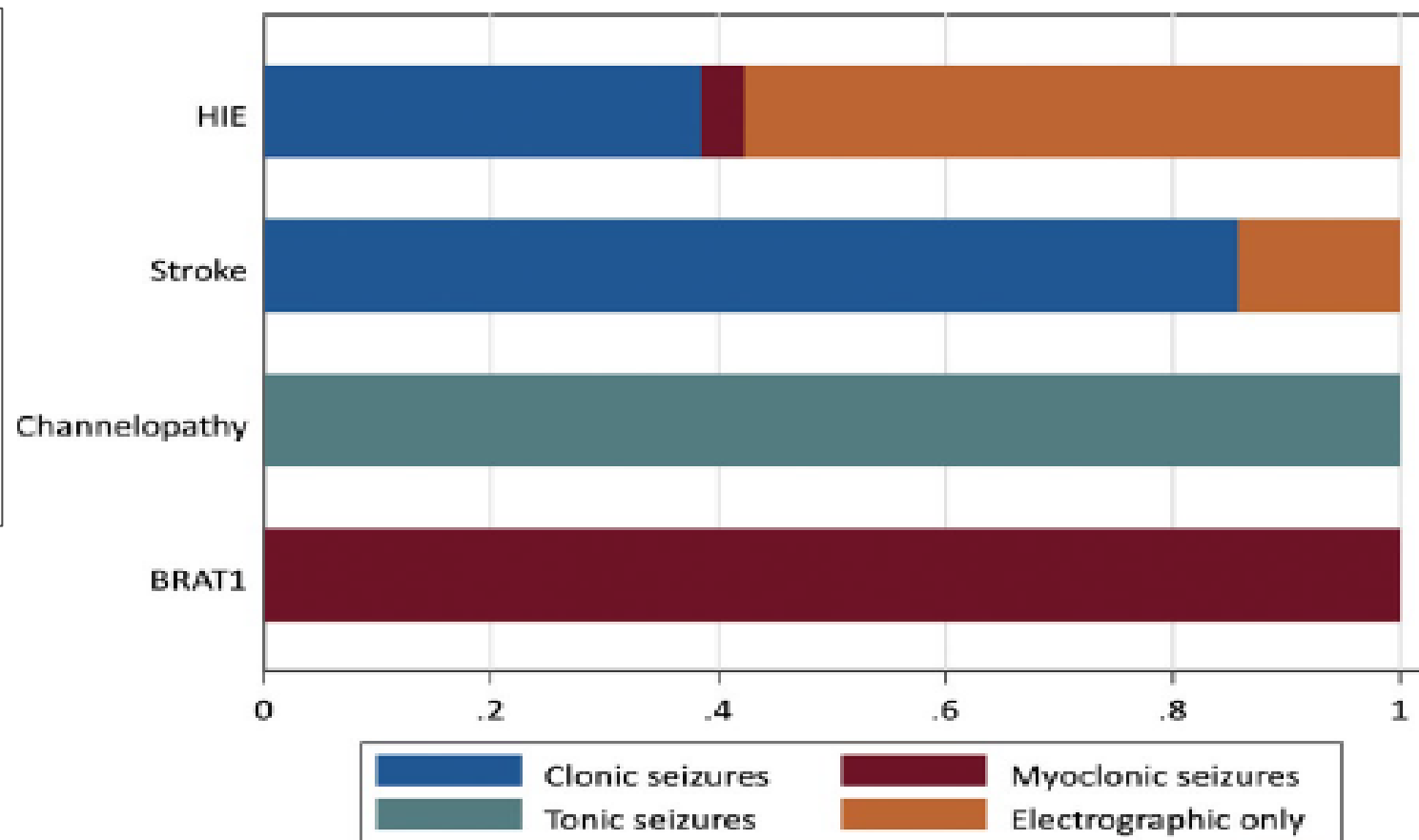
Neonatal presentation of genetic epilepsies: Early differentiation from acute provoked seizures.

Cornet MC, Morabito V, Lederer D, Glass HC, Ferrao Santos S, Numis AL, Ferriero DM, Sands TT, Cilio MR.

Epilepsia. 2021 Aug;62(8):1907-1920. doi: 10.1111/epi.16957. Epub 2021 Jun 21.



- 18/20 novorozenců s **genetickou epilepsií** mělo **tonické záchvaty** s asymetrickou tonickou posturou, někdy následované uni- či bilaterálními klony (sekvenční záchvat)
- 2/20 měly myoklonie (mutace v BRAT1)



Developmental and Epileptic Encephalopathy



- Patogenní varianty v *KCNQ2* - funkčně LoF o více než 50%
- Terapie:
 - epilepsie farmakoresistentní
 - větší pravděpodobnost bezzáchvatovosti při léčbě sodíkovými blokátory

Gabapentin treatment in a patient with KCNQ2 developmental epileptic encephalopathy

2020

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- Gabapentin aktivuje Kv7

Retigabine (ezogabine)



- Positivní alosterický modulátor *KCNQ2–5* (Kv7.2–7.5) kanálů, který otvírá K⁺ kanály
- V r. 2017 stažen z trhu pro kožní a retinální pigmentaci se ztrátou zraku

Ezogabine impacts seizures and development in patients with *KCNQ2* developmental and epileptic encephalopathy

2023

Devon Knight¹ | Sonal Mahida¹ | McKenna Kelly^{1,2}  | Annapurna Poduri¹  | Heather E. Olson¹ 

- 8 pacientů s *KCNQ2* DEE
 - 5pac. snížení frekv. záchvatů o 50%
 - 2pac. bez záchvatů
 - 1 pac. jen sporadické záchvaty (dříve 2-4 za rok)
- Vývojové zlepšení
- Zhoršení po vysazení

Neonatal nonepileptic myoclonus is a prominent clinical feature of *KCNQ2* gain-of-function variants R201C and R201H

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Epilepsia, 58(3):436–445, 2017

KCNQ2 R144 variants cause neurodevelopmental disability with language impairment and autistic features without neonatal seizures through a gain-of-function mechanism

2022



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Patient	Age at last FU	KCNQ2 variant	Degree of ID (DSM-V)	Behavioural phenotype	Current level of functioning	Onset-age of epilepsy	Episodes with reduced responsiveness of unclear origin	EEG sleep-activated epileptiform activity
1	4.5y	p.R144W	Mild	Features of ASD and ADHD	Speaks words, walks independently	/		Yes
2	6y	p.R144W	Mild to moderate	Features of ADHD	Speaks sentences, walks independently	/		No
3	4.5y	p.R144W	Mild to moderate	Features of ASD and ADHD	Speaks words, walks independently	/		No sleep-EEG
4	11y	p.R144W	Mild to moderate	Features of ASD	Speaks short sentences, walks independently	/		Yes
5	21y	p.R144W	Moderate	Features of ASD and aggressive behavior	Speaks short sentences, walks independently	/	Yes (3-6y)	No sleep-EEG
6	8y	p.R144W	Moderate	Features of ASD	Speaks words, walks independently	/		Yes
7	7.5y	p.R144W	Moderate	Features of ASD	Speaks short sentences, walks independently	/		No
8	27y	p.R144W	Severe	Features of ASD and ADHD	Nonverbal, walks independently	5y		Yes
9	3.5y	p.R144W	Severe	Normal	Nonverbal, cannot sit or walk independently	4m		Yes
10	4y	p.R144Q	Severe	Aggressive behavior	Nonverbal, cannot sit or walk independently	/	Yes (12m)	No
11	14y	p.R144Q	Severe	Features of ASD and ADHD	Nonverbal, walks independently	6m	Yes	Yes
12	14y	p.R144Q	Severe	Normal	Nonverbal, sits independently	18m	Yes	No sleep-EEG
13	26y	p.R144Q	Severe	Features of ASD and ADHD	Speaks words, walks independently	8m		No
14	4y	p.R144Q	Severe	Features of ASD and ADHD, aggressive behavior	Speaks words, sits independently	/		Yes
15	3y9m	p.R144Q	Severe	Normal	Nonverbal, sits independently	2y	Yes	Yes

Table 1: Overview of clinical features of patients with KCNQ2 R144 gain-of-function variants.

Abbreviations: ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; EEG = electroencephalogram; FU = follow-up; ID = intellectual disability; M = month; Y = year.

We have previously shown that the KCNQ2 R144Q variant, identified in a single patient, results in a GoF effect.⁹ Here, we investigated the phenotypic spectrum associated with KCNQ2 variants at the R144 position by describing detailed clinical features of 15 patients, and summarizing published clinical data on 5 additional cases. To highlight potential genotype-phenotype correlations, we compared the functional properties of Kv7.2 R144W and R144G mutant subunits with those of the previously described R144Q.⁹ At last, we demonstrate that amitriptyline inhibits channels carrying both wild-type and mutant Kv7.2 R144Q subunits, suggesting a potential targeted treatment for patients with KCNQ2 R144 variants.

Shrnutí terapie u epilepsií s patogenní variantou v *KCNQ2*



LoF	SLN(F)E		nic nebo PB nebo CBZ	
	DEE		blokátory sodíkového kanálu	CBZ
				GBP, retigabin?
GoF	neonatální encefalopatie s ne-epi myoklonem	patogenní varianty s vazbou na 201.pozici AK	farmakoresistentní	
	DEE s pozdějším začátkem	patogenní varianty s vazbou na 144. pozici AK	farmakoresistentní	amitriptylin?

Funkční dopad patogenní varianty má vliv na volbu ASM!
Úprava terapie funguje i ve vyšším věku pacienta!
Genetické vyšetření má smysl i u pacientů v dospělém věku!