JOURNAL READING

Clinical and Genetic Features in Patients With Reflex Bathing Epilepsy

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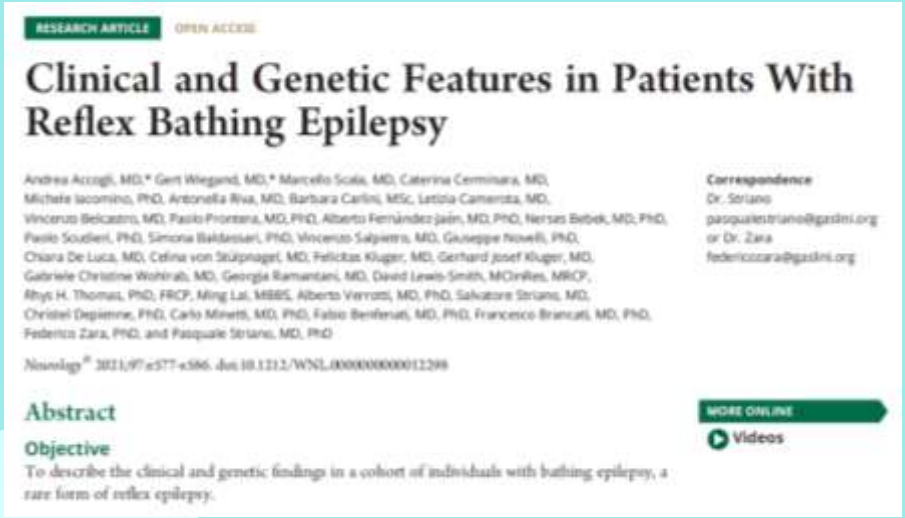

RESEARCH ARTICLE OPEN ACCESS

Clinical and Genetic Features in Patients With Reflex Bathing Epilepsy

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Abstract

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Objective
To describe the clinical and genetic findings in a cohort of individuals with bathing epilepsy, a rare form of reflex epilepsy.

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Clinical and Genetic Features in Patients With Reflex Bathing Epilepsy

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PENULIS
Accogli, *et.al*

ABSTRAK

Abstract

Objective

To describe the clinical and genetic findings in a cohort of individuals with bathing epilepsy, a rare form of reflex epilepsy.

Methods

We investigated by Sanger and targeted resequencing the *SYN1* gene in 12 individuals from 10 different families presenting with seizures triggered primarily by bathing or showering. An additional 12 individuals with hot-water epilepsy were also screened.

Results

In all families with bathing epilepsy, we identified 8 distinct pathogenic or likely pathogenic variants and 2 variants of unknown significance in *SYN1*, 9 of which are novel. Conversely, none of the individuals with hot-water epilepsy displayed *SYN1* variants. In mutated individuals, seizures were typically triggered by showering or bathing regardless of the water temperature. Additional triggers included fingernail clipping, haircutting, or watching someone take a shower. Unprovoked seizures and a variable degree of developmental delay were also common.

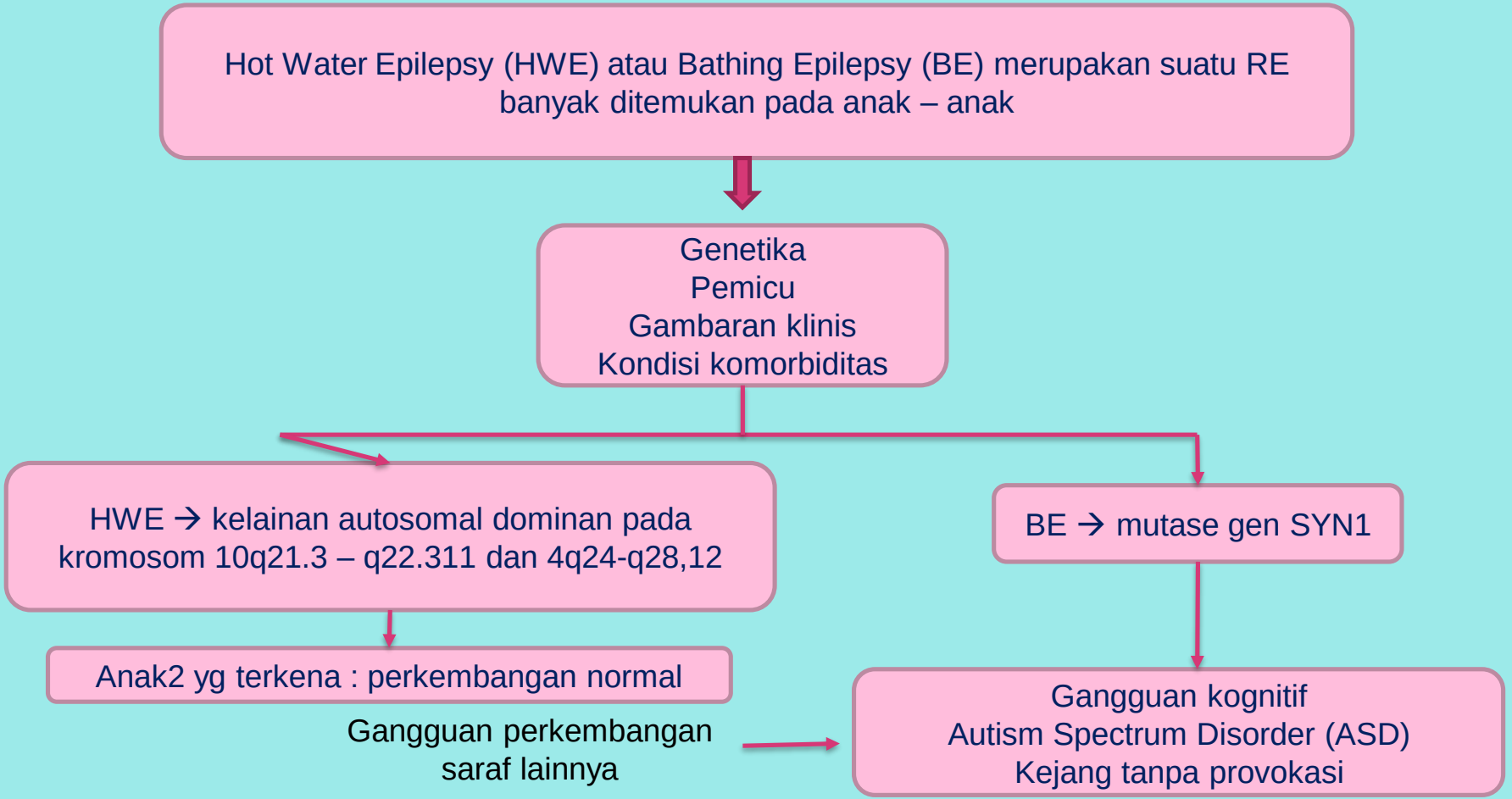
Conclusion

Bathing epilepsy is genetically distinct reflex epilepsy caused mainly by *SYN1* mutations.

PENDAHULUAN

Epilepsi reflex (RE) merujuk pada kondisi kejang berulang yang dipicu oleh stimulus eksternal ataupun internal

Stimulus dan faktor genetik diyakini menjadi penyebab terjadinya RE sehingga terjadi hipereksitabilitas pada area kortex. Hanya beberapa gen penyebab yang telah diidentifikasi pada manusia


Hot Water Epilepsy (HWE) atau Bathing Epilepsy (BE) merupakan suatu RE banyak ditemukan pada anak – anak
Genetika
Pemicu
Gambaran klinis
Kondisi komorbiditas
HWE → kelainan autosomal dominan pada kromosom 10q21.3 – q22.311 dan 4q24-q28,12
BE → mutase gen SYN1
Anak2 yg terkena : perkembangan normal
Gangguan perkembangan saraf lainnya
Gangguan kognitif
Autism Spectrum Disorder (ASD)
Kejang tanpa provokasi

Temuan klinis dan genetic didapatkan 12 individu dari 10 keluarga dipicu oleh BE. Analisis komprehensif dari cohort besar dan case reported dalam literatur menunjukkan bahwa BE merupakan RE yang secara genetik SYN1 sebagai penyebabnya.

METODE

DESAIN PENELITIAN DAN REKRUTMEN PARTISIPAN

- Didaftarkan 21 sukarelawan dari 10 keluarga berbeda dengan RE dipicu mandi melalui Network Therapy of Rare Epilepsy
- Dokumentasi via video-EEG atau video direkam sendiri
- Data klinis, temuan genetik, epilepsi, dan respon pengobatan melalui kuesioner elektronik anonim
- Rekaman interiktal/iktal-EEG, MRI otak, dan neuropsikological test ditinjau secara terpusat
- Penilaian neuropsikologi dan perilaku melalui skala

INVESTIGASI GENETIK

- DNA genom diisolasi dari leukosit darah tepi
- Analisis gen target SYN1 metode Sanger
- Varians diklasifikasikan berdasarkan American College of Medical Genetics and Genomics guidelines

METODE

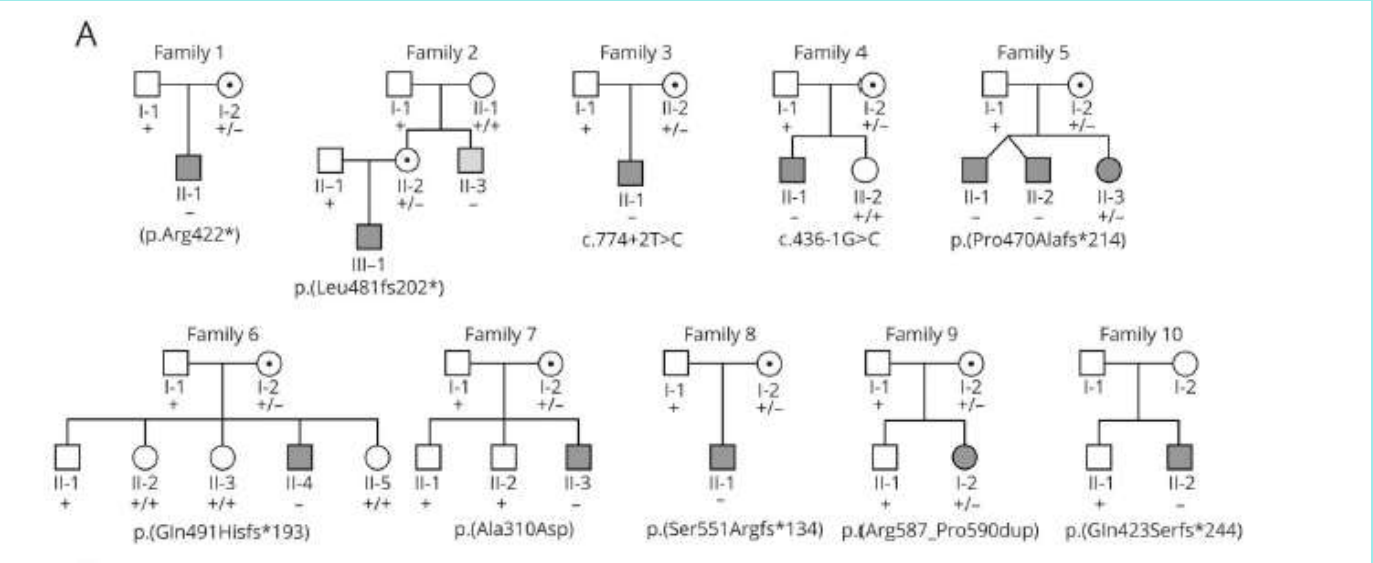
Persetujuan Protokol, Pendaftaran, dan Consents

- Etik disetujui daru IRCCS “G. Gaslini” Institute (Genova, Italy)
- Diterima persetujuan tertulis dari semua pasien atau wali yang berpartisipasi dalam penelitian ini

KETERSEDIAAN DATA

- Deskripsi klinis, metode pengujian genetic, RRG, dan tabel kasus yang dilaporkan sebelumnya dengan BE dan HWE tersedia di https://datadryad.org/stash/dataset/doi:10.5061/dryad.w0vt4b8qr
- Tidak semua data tercantum untuk umum

HASIL

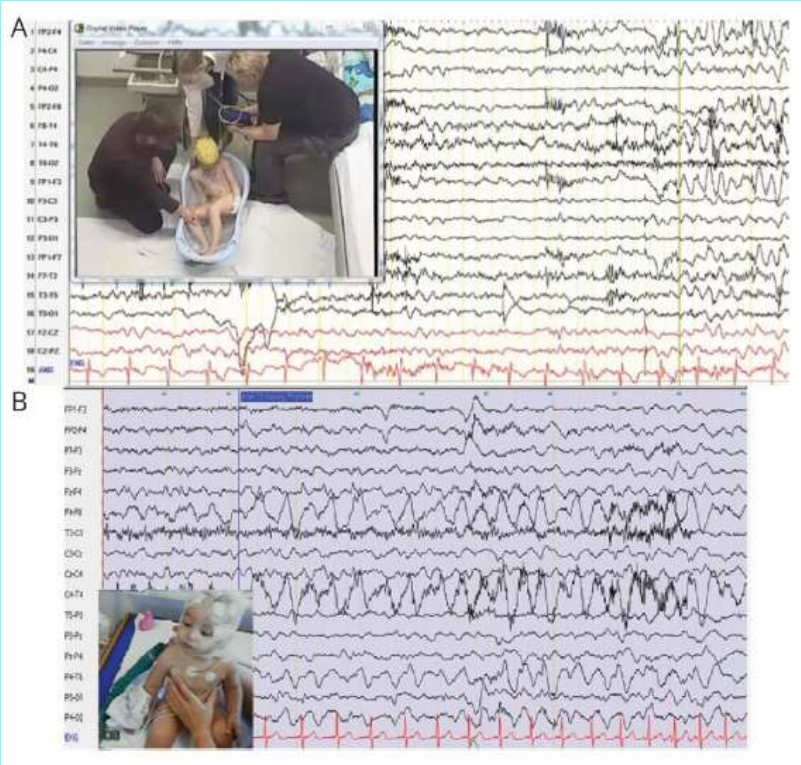


CLINICAL FINDINGS

Dirangkum pada tabel 1

- Semua kecuali 2 individu adalah laki – laki
- Semua individu memiliki epilepsy fokal dengan gangguan kesadaran dipicu mandi / berendam TIDAK berkaitan dengan suhu air
- Beberapa dipicu faktor lainnya seperti menggosokan handuk setelah mandi, melihat / memikirkan mandi, memotong kuku, potong rambut
- 1 org ada peningkatan kontrol kejang ketika mandi biasa daripada berendam air hangat
- Onset kejang yang diprovokasi berkisar usia 8 bulan – 15 tahun dengan frekuensi mingguan - bulanan

HASIL



- Semua participant menerima obat antikejang → partisipan memiliki respon yang memuaskan terutama pada Clobazam atau Asam valporat

- Gelombang EEG iktal → menunjukkan aktivitas theta polimorfik tegangan tinggi di area frontal temporal pada 2 peserta
- MRI otak dilakukan dengan tidak ada temuan kelainan

Table 1 Genetic and Phenotypic Features of Subjects With *SYN1* Variants and BE

	Family 1	Family 2	Family 3	Family 4	Family 5			Family 6	Family 7	Family 8	Family 9	Family 10
	II:1	II:1	II:1	II:2	II:1	II:2	II:3	II:4	II:3	II:1	II:2	IV:2
Age, sex	18 y M	3 y M	9 y M	15 y M	2.5 y M	2.5 y M	7 y F	5.5 y M	2 y M	13 y M	5 y F	47 y M
***SYN1* variant (NM_006950.3)**	c.1264C>T p.(Arg422*)	c.1439dupC p.(Leu481fs202*)	c.774+2T>C	c.436-1G>C	c.1406dupA p.(Pro470Alafs*214)			c.1472_1473insT p.(Gln491Hisfs*193)	c.929C>A p.(Ala310Asp)	c.1647_1650dupCGCC p.(Ser551Argfs*134)	c.1760_1771dup p.(Arg587_Pro590dup)	c.1266delA p.(Gln423Serfs*244)
Detection analysis/ Segregation	Sanger sequencing De novo	Sanger sequencing Maternal	Sanger sequencing Maternal	Sanger sequencing Maternal	WES Maternal			Gene panel Maternal	Sanger sequencing Maternal	Sanger sequencing Maternal	WES Maternal	Gene panel Presumed maternal
FH of BA	No	Yes, maternal uncle	No	No	Yes, sister	Yes, sister	Yes, brothers	No	No	No	Yes, maternal aunt	Yes, 7 maternal male relatives
Development	Speech delay, aggressive behavior, ADHD	Speech delay, hyperactivity	GDD, moderate ID, ASD, motor stereotypies, aggressive behavior, echolalia	Normal	Mild GDD, speech delay, ADHD	Mild GDD, speech delay, ADHD	Mild GDD, speech delay, autistic features	GDD, moderate ID, ASD, ADHD	Normal	GDD, mild ID, ASD, motor stereotypies ADHD	GDD, severe ID, ADHD	Mild GDD, speech delay, mild ID, autistic traits
Age at RE onset	5 y	2 y	7 y	8 y	22 mo	14 mo	2 y	4 y 7mo	1 y 3mo	8 mo	8 mo	15 y
RE onset	After showering, rubbing with towel, watching his sister having a shower	During or after bathing	During or after showering, rubbing with towel	During showering (pouring water over the head)	During bathing	During bathing	During bathing	After bathing/ showering, haircutting, fingernail clipping, watching someone while bathing, idea of bathing	During or after bathing, hair washing	After bathing, showering, fingernail clipping	During or after bathing/ showering	During immersion of the feet in water and during febrile events illnesses.
Features	Impaired awareness, pallor, cyanosis, oral automatisms, hypotonia	Impaired awareness, lip cyanosis, buccal automatisms, hypertonus	Impaired awareness, buccal automatisms, lip cyanosis, hypersalivation, hypotonus	Impaired awareness, lip cyanosis, focal to bilateral TCS	Impaired awareness, focal to bilateral TCS	Impaired awareness, focal to bilateral TCS	Focal with impaired awareness	Autonomic seizures with apnea, cyanosis, loss of consciousness, automatisms	Autonomic features, atonic seizures, pallor, staring, cyanosis	Autonomic seizures with apnea, smacking, salivation, cyanosis	Autonomic seizures, fixed gaze, pausing, myoclonus, pallor, cyanosis, orobuccal automatisms	Focal impaired awareness, orolingual automatism, salivation and spitting, right hand tapping, leftward head and gaze, disorientation with automatisms (e.g., whistling and kissing)
Seizure frequency at the onset	Weekly	Monthly	1–2/wk	Weekly	Weekly	Weekly	Weekly	2–8/mo	1–2/wk	2–3/wk	2–3/wk	1–2/wk

HASIL

Table 1 Genetic and Phenotypic Features of Subjects With *SYN1* Variants and BE *(continued)*

	Family 1	Family 2	Family 3	Family 4	Family 5			Family 6	Family 7	Family 8	Family 9	Family 10
	II:1	II:1	II:1	II:2	II:1	II:2	II:3	II:4	II:3	II:1	II:2	IV:2
Febrile seizure	Yes (4 y 9 mo)	No	No	No	No	No	No	No	Yes (3 y)	No	No	Yes, between 9 and 18 mo
Other seizures	Nocturnal TCS at 6 y	No	No	No	Focal impaired awareness seizures, 2.5 y	Focal impaired awareness seizures, 2 y	Focal impaired awareness seizures, 9 mo	Nocturnal autonomic seizures, at 5y	Nocturnal autonomic seizures, 1 y 3 mo	Nocturnal autonomic seizures, TCS SE, 7 y	Infantile spasms, 8 mo; TCS with automatism, 2 y; atonic atypical absence seizures	Focal to bilateral TCS; nocturnal TCS in cluster
EEG interictal	R temporal, L anterior temporal	L frontotemporal	R central, temporal	Normal	Bilateral temporal	Bilateral temporal	Theta activity over the right temporal regions	Bilateral centrotemporal	Normal	R and L temporal	Bursts of slow spike-wave	Twice, normal in adulthood
Ictal	NA	NA	NA	NA	NA	NA	NA	Rhythmic theta seizure pattern right temporal	Rhythmic theta seizure pattern right temporal	Rhythmic theta left temporal	Beta diffuse	NA
ASMs	CLB, VPA	CLB, VGB, CBZ, CLB	CLB	NA	VPA	VPA	VPA	VPA, STM, LTG	CBZ	OXC, STM, VPA, LTG	LTG, VPA, VGB, LAC, LEV, BRV, ZNS, steroids, KD, CBL, RUF	CBZ, LTG, VPA
Response to medications	Decreased seizures frequency	Partial response	Decreased seizures frequency	NA	Poor response	Poor response	Seizure-free	No	Seizure-free, avoidance of warm water	Seizure-free	Decreased seizure frequency CBL, RUF, BRV)	VPA and avoidance of warm water on his feet

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = antiseizure medication; BE = bathing epilepsy; BRV = brivaracetam; CBZ = carbamazepine; CLB = clobazam; FH = family history; GDD = global developmental delay; GTCS = generalized tonic-clonic seizures; ID = intellectual disability; KD = ketogenic diet; LAC = lacosamide; LEV = levetiracetam; LTG = lamotrigine; NA = not available; OXC = oxcarbazepine; RE = reflex epilepsy; RUF = rufinamide; SE = status epilepticus; STM, sulthiame; TCS = tonic-clonic seizures; VGB = vigabatrin; VPA = valproic acid; WES = whole-exome sequencing; ZNS = zonisamide.
Vagus nerve stimulator was also placed, resulting in a further decrease in the frequency of unprovoked seizures but not affecting bathing seizures.

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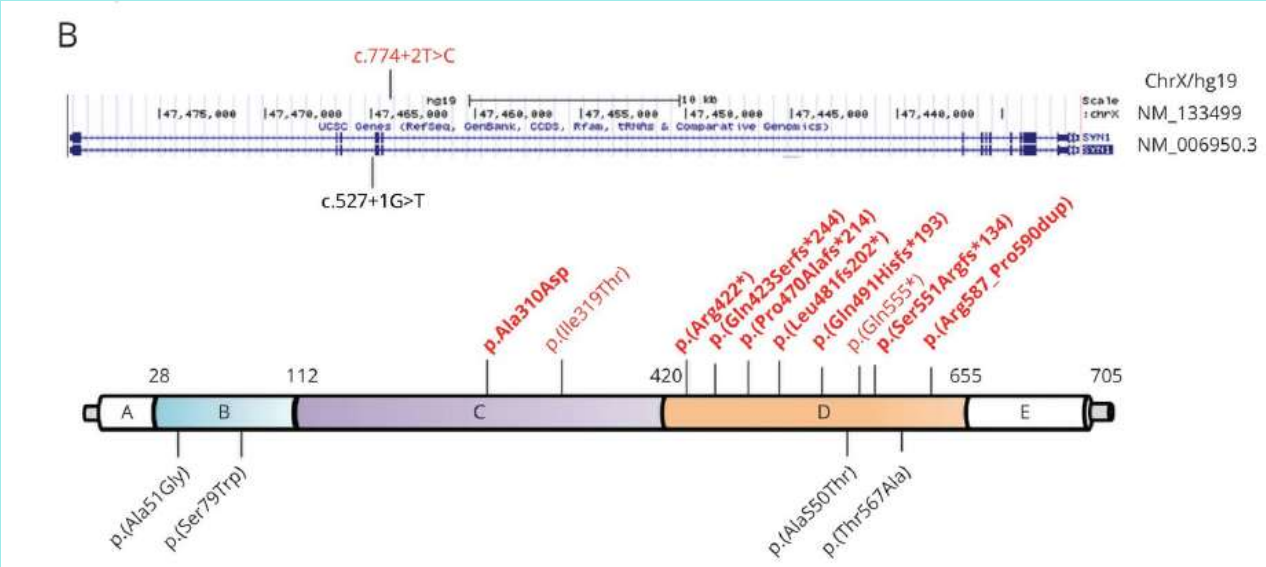


HASIL

Genetic Findings

- Teridentifikasi 8 varian pathogen berbeda pada gen SYN1
- Varian c.1264C>T p.(Arg422*) dilaporkan sebelumnya
- Semua varian lainnya diturunkan secara genetic (maternal)
- Varian c.436-1G>C dan c.774+2T>C diperkirakan sangat memengaruhi struktur protein
- 2 Varian yakni c.929C>A p.(Ala310Asp) dan c.1760_1771dup p.(Arg587_Pro590dup) tidak diketahui signifikan, tetapi diperkirakan memiliki efek merusak → hubungan klinis dengan BE mendukung sifat patogenik

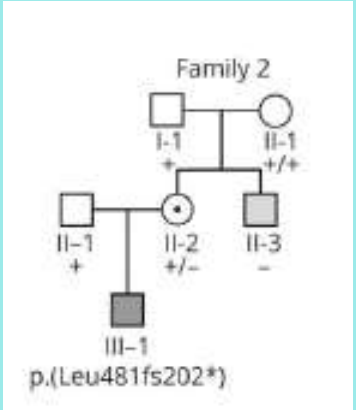
DISKUSI

- Laporan pertama pada keluarga SYN1 mengalami kejang yang dipicu mandi terjadi pada pasien pembawa varians gen SYN1 p.(W356)
- Pada tabel hasil penelitian semua pasien mengalami kejang refleks yang dipicu berendam atau shower dengan berbagai gangguan neurodevelopmental

- Mutasi nonsense, frameshift, dan splicing di dalam SYN1 diduga berperan dalam mekanisme hilangnya fungsi pada mutase SYN1 yang terkait dengan BE
- Secara keseluruhan varian SYN1 yang terkait BE dikelompokkan dalam pro-rich regulatory domain, sementara varian yang tidak terkait ditemukan dalam domain protein lainnya

DISKUSI

- Selain itu, diamati juga pada keluarga 2 terdapat variabilitas intrafamilial dimana paman dari pihak ibu (maternal) terdapat kejang tanpa provokasi dan ASD → sejalan dengan bukti sebelumnya dimana semua individu yang mengalami mutasi SYN1 memiliki gangguan perkembangan saraf dan tidak semua berkembang menjadi BE



DISKUSI

- Gambaran klinis utama dari penelitian ini dipicu BE. Semua kecuali 1 individu mengalami kejang yang dipicu mandi atau berendam terlepas dari suhu air
- 1 orang mengalami kejang berulang yang dipicu mencelupkan kaki ke air bukan menuangkan air ke kepala
- Pemicu tambahannya adalah menggosok dengan handuk basah, memotong kuku, memotong rambut
- 2 orang , kejang juga diprovokasi dengan melihat seseorang mandi / memikirkan mandi
- 2 wanita pertama dengan BE → hipotesisnya karena ada skewed X inactivation di jaringan otak

DISKUSI

SYN1 mengkodekan fosfoprotein spesifik neuron yang terlibat dalam regulasi pelepasan neurotransmitter

Peran SYN1 dalam epilepsy telah dijelaskan penelitian sebelumnya dengan model tikus → gangguan vesikel sinapsis dan gangguan pelepasan GABA

Hipereksitabilitas → kejang

Patofisiologi BE terkait SYN1 belum diketahui

Temuan pada SPECT ictal pada beberapa individu disebutkan keterlibatan korteks insular

Terganggunya kontrol motoric, fungsi kognitif, gejala otonom

Demikian, mutase SYN1 menyebabkan ketidakseimbangan excitatory dan inhibitory → ke area insular shg kejang setelah terkena air

DISKUSI

- Laporan HWE pada individu pembawa varian SYN1 diperdebatkan apakah sama dengan BE
- HWE diinduksi dengan mandi air >37C → kejang terjadi saat airpanas dituangkan ke kepala atau saat individu meninkmati situasi mandi air panas
- Studi SPECT menunjukkan ictal hypermetabolic uptake pada struktur medial temporal dan hipotalamus
- Meskipun patofisiologi HWE masih belum diketahui, telah diasumsikan keterkaitan pusat termoregulasi di hipotalamus yang memicu kejang

Secara keseluruhan BE dan HWE menunjukkan temuan tekait stimulus somatosensori daripada suhu air → oleh karena itu kejang reflex yang timbul setelah paparan air dipicu oleh rangsangan somatosensory air, dan suhu air hanya memainkan perang yang membingungkan

REFERENCES

References

1. Okudan ZV, Özkara Ç. Reflex epilepsy: triggers and management strategies. *Neuropsychiatr Dis Treat.* 2018;14:327-337.
2. Striano S, Coppola A, del Gaudio L, Striano P. Reflex seizures and reflex epilepsies: old models for understanding mechanisms of epileptogenesis. *Epilepsy Res.* 2012; 100(1-2):1-11.
3. Koepp MJ, Caciagli L, Pressler RM, Lehnertz K, Beniczky S. Reflex seizures, traits, and epilepsies: from physiology to pathology. *Lancet Neurol.* 2016;15(1):92-105.
4. Michelucci R, Mecarelli O, Bovo G, et al. A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures. *Neurology.* 2007;68(24):2150-2151.
5. Galizia EC, Myers CT, Leu C, et al. CHD2 variants are a risk factor for photosensitivity in epilepsy. *Brain.* 2015;138(pt 5):1198-1207.
6. Italiano D, Striano P, Russo E, et al. Genetics of reflex seizures and epilepsies in human and animals. *Epilepsy Res.* 2016;121:47-54.
7. Vlaskamp DRM, Shaw BJ, Burgess R, et al. SYNGAP1 encephalopathy: a distinctive generalized developmental and epileptic encephalopathy. *Neurology.* 2019;92(2): e96-e107.
8. Zeki G, Ilker IH, Hidir UU, Zeki O. Hot water epilepsy: seizure type, water temperature, EEG findings and treatment. *Neurologist.* 2010;16(2):109-112.

9. Mosquera-Gorostidi A, Azcona-Garraza G, Yoldi-Petri ME, García de Gurtubay I, Aguilera-Albesa S. Ictal video-electroencephalography findings in bathing seizures: two new cases and review of the literature. *Pediatr Neurol.* 2019;99:76-81.
10. Bebek N, Günes C, Gokyigit A, Baykan B, Ozkara C, Dervent A. Hot water epilepsy: clinical and electrophysiologic findings based on 21 cases. *Epilepsia.* 2001;42(9):1180-1184.
11. Ratnapriya R, Satishchandra P, Kumar SD, Gadre G. A locus for autosomal dominant reflex epilepsy precipitated by hot water maps at chromosome 10q21.3-q22.3. *Hum Genet.* 2009;125(5-6):541-549.
12. Ratnapriya R, Satishchandra P, Dilip S, Gadre G. Familial autosomal dominant reflex epilepsy triggered by hot water maps to 4q24-q28. *Hum Genet.* 2009;126(5):677-683.
13. Cesca F, Baldelli P, Valtorta F, Benfenati F. The synapsins: key actors of synapse function and plasticity. *Prog Neurobiol.* 2010;91(4):313-348.
14. Farisello P, Boido D, Nieus T, et al. Synaptic and extrasynaptic origin of the excitation/inhibition imbalance in the hippocampus of synapsin I/II/III knockout mice. *Cereb Cortex.* 2013;23(3):581-593.
15. Garcia CC, Blair HJ, Seager M, et al. Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. *J Med Genet.* 2004;41(3):183-186.
16. Guarnieri FC, Pozzi D, Raimondi A, et al. A novel SYN1 missense mutation in non-syndromic X-linked intellectual disability affects synaptic vesicle life cycle, clustering and mobility. *Hum Mol Genet.* 2017;26(23):4699-4714.
17. Nguyen DK, Rouleau I, Sénéchal G, et al. X-linked focal epilepsy with reflex bathing seizures: characterization of a distinct epileptic syndrome. *Epilepsia.* 2015;56(7):1098-1108.
18. Sirsi D, Armstrong D, Muñoz-Bibiloni J, Redondo B. SYN1 gene mutation in a child with focal epilepsy and reflex bathing seizures. *J Pediatr Epilepsy.* 2017;06(2):119-124.
19. Ameen RB, Barker L, Zafar MS. Electroencephalography findings in bathing reflex epilepsy. *Pediatr Neurol.* 2020;102:81.
20. Peron A, Baratang NV, Canevini MP, Campeau PM, Vignoli A. Hot water epilepsy and SYN1 variants. *Epilepsia.* 2018;59(11):2162-2163.
21. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424.
22. Fassio A, Patry L, Congia S, et al. SYN1 loss-of-function mutations in autism and partial epilepsy cause impaired synaptic function. *Hum Mol Genet.* 2011;20(12):2297-2307.
23. Lignani G, Raimondi A, Ferrea E, et al. Epileptogenic Q555X SYN1 mutant triggers imbalances in release dynamics and short-term plasticity. *Hum Mol Genet.* 2013; 22(11):2186-2199.
24. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain.* 1996;22(3):229-244.
25. von Stülpnagel C, Hartlieb T, Borggräfe I, et al. Chewing induced reflex seizures ("eating epilepsy") and eye closure sensitivity as a common feature in pediatric patients with SYNGAP1 mutations: review of literature and report of 8 cases. *Seizure.* 2019;65:131-137.
26. Striano P, Huppke P. A synaptic protein defect associated with reflex seizure disorder. *Neurology.* 2019;92(2):63-64.
27. Subki AH, Alaamari AS, Jan FM, Moria FA, Jan MM. Reflex seizures triggered by diaper change in Dravet syndrome. *Can J Neurol Sci.* 2016;43(4):585-587.
28. Arican P, Dundar NO, Cavusoglu D, Ozdemir TR, Gencpinar P. Somatosensory reflex seizures in a child with epilepsy related to novel SCN1A mutation. *Childs Nerv Syst.* 2017;33(4):677-680.
29. Satishchandra P, Sinha S. Hot-water epilepsy: from bench to bedside. *Ann Indian Acad Neurol.*2013;16(2):137-143.
30. Lisovoski F, Prier S, Koskas P, et al. Hot-water epilepsy in an adult: ictal EEG, MRI and SPECT features. *Seizure.* 1992;1(3):203-206.
31. Patel M, Satishchandra P, Aravinda H, Bharath RD, Sinha S. Hot water epilepsy: phenotype and single photon emission computed tomography observations. *Ann Indian Acad Neurol.* 2014;17(4):470-472.
32. Satishchandra P, Kallur KG, Jayakumar PN. Inter-ictal and ictal 99m TC ECD SPECT scan in hot-water epilepsy. *Epilepsia.* 2001;42(suppl):158.
33. Satishchandra P, Shivaramakrishana A, Kaliaperumal VG, Schoenberg BS. Hot-water epilepsy: a variant of reflex epilepsy in southern India. *Epilepsia.* 1988;29(1):52-56.
34. Satishchandra P. Hot-water epilepsy. *Epilepsia.* 2003;44(suppl 1):29-32.
35. Pulvermüller F. Brain mechanisms linking language and action. *Nat Rev Neurosci.* 2005;6(7):576-582.

Thank you!