Clinical/Scientific Notes

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FHF1 (FGF12) EPILEPTIC ENCEPHALOPATHY

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Voltage-gated sodium channels (Na_vs) are mainstays of neuronal function, and mutations in the genes encoding CNS Na_vs ($Na_v1.1$ [*SCN1A*], $Na_v1.2$ [*SCN2A*], $Na_v1.3$ [*SCN3A*], and $Na_v1.6$ [*SCN8A*]) are causes of some of the most common and severe genetic epilepsies and epileptic encephalopathies (EE).[1] Fibroblast-growth-factor homologous factors (FHFs) compose a family of 4 proteins that interact with the C-terminal tails of Na_vs to modulate the channels' fast, and long-term, inactivations.[2] *FHF2* mutation is a rare cause of generalized epilepsy with febrile seizures plus (GEFS+).[3] Recently, a de novo *FHF1* mutation (p.R52H) was reported in early-onset EE in 2 siblings.[4] We report 3 patients from unrelated families with the same *FHF1* p.R52H mutation. The 5 cases together frame the FHF1 R52H EE from infancy to adulthood. As discussed below, this gain-of-function disease may be amenable to personalized therapy.

Patient 1 (P1, table) is a 3-year-old boy. Convulsive seizures began on day 2 of his life and remain intractable, with frequent status epilepticus (SE) manifesting as generalized or right-sided facial seizures. His EEGs show slow backgrounds and multifocal epileptiform discharges (figure e-1 at Neurology.org/ng). Multiple antiepileptic drug (AED) regimens failed, but he is currently at his best on a combination of the ketogenic diet and medications indicated in the table. He has severe global developmental delay, is nonverbal, has poor visual and social interaction, just started rolling slightly and sitting with support, and is tube-fed. He has generalized hypotonia with head lag and does not track. He suffers from chronic constipation. MRI at onset was normal, and at 2 years revealed widened ventricles and pericerebral CSF spaces (figure e-2A).

Patient 2 (P2) is a 16-year-old girl with intractable seizures since age 6 weeks and frequent SE. Seizures included generalized tonic-clonic (GTC) and partial seizures with left-sided facial twitching and lip-smacking (figure e-3). Phenytoin has been part of her AEDs, and relatively efficacious, since age 6 years. Since age 7, she develops 24 hours of severe ataxia after every GTC, which then gradually improves. Vagal nerve stimulation substantially improved seizure, and ataxia, intensities, and frequencies. MRI at 16 months was unremarkable but at 8 years showed cerebellar atrophy (figure e-2B). She suffers from chronic constipation. She has severe cognitive impairment with single words, has normal motor development, and ambulates. She needs help with all activities of daily living.

Patient 3 (P3) is an 18-year-old girl with intractable epilepsy since day 2 of her life with frequent SE. Seizures include leftward head deviation followed by generalized convulsion. EEGs were slow with multifocal spikes in infancy and Lennox-Gastaut–like in early childhood. She suffers from chronic constipation, hypohydrosis, and reduced lacrimation, suggesting autonomic dysfunction. She has moderate intellectual disability and can read simple books. She ambulates with a spastic circumductive gait and has substantial heel cord tightness. Current therapies (table) include vagal nerve stimulation. MRI at present shows bilateral mesial temporal sclerosis and mild prominence of cerebellar folia, findings not present in MRIs from early childhood (figure e-2C).

All 3 patients had the same de novo *FHF1* NM_004113.5:c.155G>A, p.R52H mutation detected by whole-exome or whole-genome sequencing and confirmed by Sanger sequencing, and no other relevant de novo change. The table summarizes their clinical features and those of the recently published[4] original sib-pair. Salient features of the latter pair include neonatal-onset intractable epilepsy, profound intellectual disability, severe feeding difficulties, MRI initially unremarkable and subsequently exhibiting cerebellar atrophy, ataxia, and death in SE.[4]

Based on 5 patients, the core FHF1 R52H disease comprises neonatal-onset persistent intractable epilepsy and moderate-to-severe intellectual disability. Radiologically, neurodegeneration, especially cerebellar, is present, which, beyond a mutational consequence appears to be aggravated by the severity and frequency of SE. It may also be exacerbated by treatment of SE. All 4 patients with cerebellar atrophy, including the original 2, were on phenytoin (table), repeatedly loaded and subsequently chronically maintained because of relative success in SE

Table Phenotypic features of 5 patients with FHF1 R52H epileptic encephalopathy

	O1	O2	P1	P2	P3
Current age and sex	Died age 7 y, female	Died age 3.5 y, male	3 y, male	16 y, female (DDD patient 251978)	18 y, female
Age at first seizure	2 wk	4 wk	2 d	6 wk	2 d
Status epilepticus	Frequent	Frequent	Frequent	Frequent	Frequent
Seizure types	Tonic seizures	Tonic seizures	GTC; right facial twitching	Myoclonic; GTC; partial motor seizures, lip-smacking, left facial twitching	Partial motor seizures with retained consciousness; left versive seizures followed by GTC
Interictal EEG findings	High-voltage slow activity with multifocal epileptiform discharges	High-voltage slow activity with multifocal epileptiform discharges	High-voltage slow activity with multifocal epileptiform discharges	Slow background with bilateral, right more than left, epileptiform discharges	Slow background with bilateral, right more than left, epileptiform discharges
Ictal EEG findings	Generalized high-voltage spike, sharp wave and spike waves followed by long suppression of background		Onset of high-amplitude 1.5–2 Hz rhythmic activity over right posterior head region with secondary generalization		
Current AED	AED regimen included phenytoin	AED regimen included phenytoin	Levetiracetam, phenobarbital	Phenytoin, perampanel, VNS	Phenytoin, pregabalin, perampanel, VNS
Developmental delay/ intellectual disability	Severe psychomotor retardation, nonverbal	Severe psychomotor retardation	Severe global developmental delay, nonverbal	Severe global developmental delay and intellectual disability, single words	Moderate intellectual disability, possible autism spectrum disorder
Cerebellar involvement	Cerebellar atrophy, ataxia	Cerebellar atrophy, ataxia	To date uninvolved	Episodic cerebellar ataxia from age 7 y, cerebellar atrophy on MRI from age 8	Mild cerebellar atrophy appearing in adolescence
Other neurologic abnormalities	Cerebral visual impairment	Poor visual contact	Cortical visual impairment		Heel cord tightness with spastic circumductive gait
Neurologic examination	Hypotonia, microcephaly	Hypotonia, microcephaly	Diffuse hypotonia with head lag		Normal tone, slightly hyperreflexic
Concomitant morbidities	Feeding difficulties	Feeding difficulties	Constipation and vomiting; feeding difficulties that necessitate tube feeding	Severe chronic constipation	Signs of autonomic dysfunction: hypohidrosis, reduced lacrimation; chronic constipation
MRI findings	Cerebellar atrophy at age 6 y	Cerebellar atrophy at age 3 y	Cortical atrophy between 2 mo and 2 y	Cerebellar atrophy at age 8 y	Bilateral mesial temporal sclerosis, more marked on the right; prominence of cerebellar folia
Current therapies	Unspecified but includes phenytoin (G. Buyse, MD, PhD, personal communication, April 5, 2016)	Unspecified but includes phenytoin (G. Buyse, MD, PhD, personal communication, April 5, 2016)	Ketogenic diet, levetiracetam, phenobarbital	VNS, phenytoin, perampanel	VNS, phenytoin, perampanel, pregabalin

Abbreviations: AED = antiepileptic drug; O = original 2 patients from reference 4; P = present 3 patients (P2 is from the DDD Study, ID# DDD-NGS259178); GTC = generalized tonic-clonic; VNS = vagal nerve stimulation; DDD = Deciphering Developmental Disorders.

management and prevention. It may be cautious to use alternative medications, where possible, until this putative phenytoin cerebellar iatrogenicity is clarified.

Siekierska et al.[4] demonstrated in vitro and in vivo that R52H is a toxic gain-of-function mutation. To date, thousands of patients with EE have undergone exome sequencing. Our rare finding of an FHF1 mutation suggests that FHF1 R52H might be a mutation-specific disease. It is possible that future *FHF1* mutations with similar effects will be identified, but these would be expected to act through similar gain-of-function mechanisms. As such, methods to downregulate the R52H and related alleles, e.g., with allele-specific antisense oligonucleotides, could prove therapeutic in this catastrophic encephalopathy.

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