Case Report

Gorlin–Goltz syndrome and epilepsy: A two-case report and review of the literature

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ABSTRACT

Gorlin–Goltz syndrome, also known as nevoid basal cell carcinoma syndrome, is a genetic disorder with several neurological, cutaneous and skeletal manifestations. Epilepsy has been previously reported as a finding in Gorlin–Goltz syndrome but remains ill-described in the context of this disease. We report two new patients with Gorlin–Goltz syndrome featuring epilepsy and review the existing literature on the topic.

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1. Introduction

Gorlin–Goltz syndrome is an autosomal dominant disorder caused by microdeletions of the chromosomal sub-band *9q22.3* affecting the *patched-1* (*PTCH-1*) gene, a tumor suppressor gene involved in the Sonic Hedgehog (SHH) pathway for cell differentiation [1]. Main clinical features include multiple basal cell carcinomas, odontogenic keratocysts of the jaw, palmar or plantar pits, bifid ribs, and bilamellar calcification of the falx cerebri. Apart from the latter, other neurological findings have been reported in some patients such as macrocephaly, congenital hydrocephalus, bridging of the sella turcica, meningioma and medulloblastoma [2]. It may also be associated with epilepsy although this has not been well described [3–7]. The limited number of publications on this topic describe variable seizure semiology (apneic spells, infantile spasms, focal unaware seizures and generalized tonico-clonic seizures) and treatment modalities (from various antiseizure drugs to epilepsy surgery). We report two patients with Gorlin–Goltz syndrome and epilepsy, and review the existing literature on the topic.

2. Case report

2.1. Case 1

A 29-year-old right-handed man was referred to our epilepsy center for drug-resistant seizures which started at age 27 years. Seizures were initially characterized by weekly episodes of left hemibody numbness but eventually evolved into daily to weekly episodes that started with a vague aura of fatigue and dizziness followed by facial flushing, impaired awareness, incoherent speech, and manual automatisms. His neurological exam was normal except for macrocephaly and slight stuttering. Past medical history was significant for Asperger's syndrome and Gorlin–Goltz syndrome with multiple basal cell carcinomas and odontogenic keratocysts. Brain MRI disclosed atrophy of the right temporal lobe (including the hippocampus) in addition to calcifications of the falx cerebri and the tentorium cerebelli, a cavum vergae, a cavum septum pellicum, and atrophy of the vermis. Fluorodeoxyglucose-PET scan revealed right temporal hypometabolism. However, seizures recorded during surface EEG monitoring suggested a left temporal onset for 13 seizures versus a right temporal onset for two. A subsequent invasive EEG study (sampling notably both temporal and insular lobes as well as some frontal and parietal areas) identified active interictal spiking over temporal and insular regions bilaterally, numerous left hippocampal electrical and electroclinical seizures, and three right hippocampal seizures. The patient underwent a left anterior temporal lobectomy and has been seizure-free since (FU 10 years) except for occasional complaints of 'dizziness' for 2 s without impaired awareness every two months. Post-operative neuropsychological evaluation

showed a slight decline in verbal memory. Pathological analysis of the resected tissue revealed hippocampal sclerosis.

2.2. Case 2

A 46-year-old female with Gorlin–Goltz syndrome was referred to reassess her neurological condition after being lost to follow-up for several years. Onset of seizures was at 18 years of age. Between the ages of 18 and 36 years, she mentioned having had seven or eight seizures. She has not had any seizure for the last 10 years. Back then, seizures were characterized by a burning sensation that started in her lower extremities progressing rostrally followed by impaired awareness and postictal confusion for several minutes. At the time, she was initially given phenytoin and clobazam; this combination was later replaced by valproic acid with good response. More recently (age 45 years), valproic acid was stopped in favor of levetiracetam prior to the surgical removal of a left vestibular schwannoma to minimize bleeding risks. Post-operatively, the patient elected to stop levetiracetam and has not had a seizure since (follow-up one year). Investigations performed following the onset of seizures included a CT scan showing extensive calcifications of the tentorium cerebelli and falx cerebri, an MRI showing a left vestibular schwannoma, three normal EEGs, and normal cardiac tests (ultrasound, cardiac MRI, Holter, stress-test). Prior genetic testing revealed multiple *9q22* microdeletions in the *PTCH-1* gene.

Table 1
Summary of clinical findings in cases of Gorlin–Goltz Syndrome featuring epilepsy.

	Murphy and Tenser, 1982				Hogan et al., 1996	Tachi et al., 2007	Yamamoto et al., 2009		Our cases	
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 1	Patient 1	Patient 2	Patient 1	Patient 2
Age (years)	25	29	14	9	15	0.6	12	23	29	46
Gender	F	M	M	M	F	M	M	M	M	F
Cognition	Severe MR	IQ 72	IQ 84	IQ 83	No MR	Developmental delay	Developmental delay	Severe MR	Asperger; no MR	No MR
Age at epilepsy onset (years)	2	n/a	n/a	n/a	1.1	0.4	1	3	27	18
Seizure type	Focal unaware, GTC	Unknown onset tonic–clonic	Unknown onset tonic–clonic	Unknown onset tonic–clonic	Apneic spells in infancy, focal unaware ± BTC	Infantile spasms (West syndrome)	Multifocal to BTC	Not specified	Focal unaware	Focal unaware
Current anti-seizure drugs	n/a	n/a	n/a	n/a	n/a	VPA	None (seizures improved with R F ganglioglioma resection)	Pb	LCM, PGB	None
Past anti-seizure drugs	n/a	n/a	n/a	n/a	VPA + several others not specified	ACTH, B6	CBZ, VPA	n/a	PHT, CBZ, CLB, TPM, Pb, LEV	LEV, PHT, CLB, VPA
X-ray findings	Large cranial vault, calcifications of falx cerebri, lytic lesions of the skull	Calcifications of falx cerebri	Calcifications of falx cerebri	n/a	Cervical spina bifida occulta	n/a	i/a	n/a	n/a	n/a
CT findings	n/a	n/a	n/a	n/a	Calcifications of falx cerebri and tentorium cerebelli	Calcifications of falx cerebri and tentorium cerebelli	Dilation of ventricles and calcifications of falx cerebri	n/a	n/a	Calcifications of the falx cerebri and tentorium cerebelli
MRI findings	n/a	n/a	n/a	n/a	L anterior T heterotopia	Normal	R frontal tumor (1.5cm)	n/a	R T atrophy, calcifications of falx cerebri and tentorium cerebelli, cavum vergae, cavum septum pellicum and atrophy of the vermis	L vestibular schwannoma
EEG findings	R P spikes	BiF intermittent delta	BiT paroxysmal theta	BiT paroxysmal theta	VEEG: L FT or biFT onset	Modified hypsarrythmia during sleep	Multifocal	n/a	icEEG: independent L > R T onset	3 normal EEGs
Epilepsy surgery	n/a	n/a	n/a	n/a	L ATL sparing hippocampus (sz-free post-op; FU 6 months)	n/a	R F lesionectomy	n/a	L ATL (Engel 1; FU 10 years)	n/a
Pathology	n/a	n/a	n/a	n/a	Glioneuronal and neuronal heterotopias, extensive cortical dysplasia	n/a	Ganglioglioma with desmoplasia (seizures improved; FU n/a)	n/a	L HS	n/a

ACTH: adrenocorticotropic hormone, ATL: anterior temporal lobectomy, BiF: bifrontal, BiFT: bifrontotemporal, BiT: bitemporal, BTC: bilateral tonic–clonic, CBZ: carbamazepine, CLB: clobazam, GTC: generalized tonic–clonic, F: frontal, HS: hippocampal sclerosis, LCM: lacosamide, LEV: levetiracetam, MR: mental retardation, P: parietal, Pb: phenobarbital, PHT: phenytoin, T: temporal, VPA: valproic acid.

2.3. Cases from the literature

A review of the literature identified eight previously reported cases of Gorlin–Goltz syndrome featuring seizures (6M/2F; 7 months–29 years old); (Table 1). Except for one, all had mild to severe mental retardation or developmental delay. Seizure onset was reported for 5/8 cases, all in infancy contrary to our cases (mean 1.5 years old; range 0.4–3). One patient had West syndrome with infantile spasms and modified hypsarrythmia. Another had drug-resistant focal epilepsy related to a malformation of cortical development (glioneuronal and neuronal heterotopias and extensive cortical dysplasia in the left temporal lobe) seizure-free after a left temporal lobectomy sparing the hippocampus albeit with only 6 months of postoperative follow-up. A third with multifocal spikes showed an improvement of seizure frequency after the removal of a right frontal ganglioglioma. Seizure types, semiology, EEG findings, and treatment were not well-reported for the remaining four.

3. Discussion

Gorlin–Goltz syndrome is a multisystemic genetic disease with complete penetrance and variable expressivity [8]. The prevalence of this syndrome is estimated at 1/30827 with a birth incidence of 1/18976 [9]. Major diagnostic findings in Gorlin–Goltz syndrome include development of multiple basal cell carcinomas, jaw odontogenic keratocysts, palmar and plantar pits and calcifications of the falx cerebri. Minor findings reported with this syndrome include macrocephaly, frontal bossing, bifid or extra ribs, bifid or fused vertebra, cleft lip, polydactyly, cardiac or ovarian fibromas, and medulloblastomas [2,3]. Mutations of the *PTCH-1* gene on chromosome *9q22.3* are believed to be at the molecular origin of this syndrome's pathology; mutations on *SUFU-1* or *PTCH-2* genes are less commonly encountered [2]. *PTCH-1* mutations result in a loss of function of the PTCH protein, a transmembrane receptor for the Sonic Hedgehog protein [2,10]. The unbound PTCH protein suppresses cell proliferation whereas the binding of SHH to PTCH-1 upregulates cell proliferation. Mutations of the gene are believed to impair PTCH's function of tumor suppression [11].

Here we report two cases of Gorlin–Goltz syndrome featuring epileptic seizures. Epilepsy is not considered a classical finding in Gorlin–Goltz syndrome but has been sparsely reported in the literature. Our review of the literature identified eight additional cases albeit the description of the epileptic syndrome was not always detailed. Overall, these cases reveal heterogeneity in the characteristics of the epileptic disorders seen in patients with Gorlin–Goltz syndrome. While developmental delay and mental retardation appear frequently, some have normal cognition. Seizure onset generally occurs in infancy but onset in adulthood is possible. Seizures are generally focal to bilateral tonic–clonic but infantile spasms have been reported. Epileptiform activity is not limited to a particular lobe: parietal, frontal, or temporal. Epileptogenic lesions may include focal heterotopias, gangliogliomas, and hippocampal sclerosis. Epilepsy surgery can be an option in well-selected drug-resistant patients. Obviously, all our observations are limited by its retrospective design, the small number of patients, and publication biases.

The role of SHH upregulation has been associated with the PTCH-1 receptor in the development of multiple basal cell carcinomas in Gorlin–Goltz syndrome [10]. Interestingly, SHH signaling also plays a role in embryogenesis, the formation of the central nervous system as well as neural patterning [12]. It has been shown in human and mouse-model studies that SHH is expressed in the temporal neocortex and is found to be at higher concentrations after a seizure, suggesting it might play a role in the pathogenesis of epilepsy [13]. Further investigations into the role of mutations of the 9q22 chromosome involving the PTCH-1 gene and the effect of SHH on the brain will hopefully provide a better understanding of neurological features associated with Gorlin–Goltz syndrome, notably epileptic seizures.

4. Conclusion

We describe two cases of Gorlin–Goltz syndrome with epilepsy, adding further evidence to the existing literature that there is possibly a shared molecular mechanism despite the relative heterogeneity in clinical presentation.

Ethical statement

Consent was obtained from both individuals discussed in this publication in conformity with the guidelines set out by the University of Montreal Research Center's Ethics Board.

Declaration of competing interest

The authors have no conflicts of interest to declare with respect to this publication.

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