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SHORT RESEARCH ARTICLE

Extreme late onset of genetic generalized epilepsy in older adults and the elderly: A cohort study and literature review

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Abstract

Rare case reports describe genetic generalized epilepsy (GGE) starting de novo in people ≥50 years of age (older adults and the elderly). We aimed to provide comprehensive detail of electro-clinical findings of this extremely late-onset GGE using a retrospective, single-center cohort design and a systematic review of the literature. People with de novo seizure onset ≥50 years of age with EEG and clinical history consistent with GGE were included. These 12 individuals (9; 75% females) with a median age of 56 years at seizure onset accounted for 7.9% of 152 older adults and the elderly with generalized epilepsy. Three patients only had absence seizures. A family history of epilepsy was present in 5 individuals. They had tried a median of 2 anti-seizure medications. More than 90% (11 of 12) were seizure-free for >1 year at the last follow-up, including four requiring monotherapy. Valproate was used in only two patients and levetiracetam in 75% of them. A systematic literature review revealed six papers with 10 extreme late-onset GGE cases. They similarly had good seizure outcomes but a majority were on valproate. Our study shows that rarely, late-onset epilepsy can be GGE, which mostly has a good prognosis.

KEYWORDS

anti-seizure medications, EEG, epilepsy in elderly, geriatric epilepsy

1 | INTRODUCTION

Genetic generalized epilepsy (GGE), typically seen in children and adolescents with clearly defined electro-clinical syndromes, may present during adulthood (onset ≥20 years of age). A study of first-seizure clinic patients with well-characterized GGE found that a quarter had adult-onset epilepsy.[1] However, GGE has a steep decline in incidence beyond the third decade of life. "Late-onset" GGE, defined as seizure onset after 30 years of age, accounted for less than 6% of 492 people with GGE.[2] Even rarer among the late-onset GGE cohort are individuals with seizure onset after 50 years of age, noted in 0.6% to 4.1% of patients.[1,2] The literature lacks details on this unique group of individuals with "extreme late-onset" GGE. The available data are only present in the form of case reports.[3–6] In a rapidly aging, healthier population with longer life expectancies than ever before, we are likely to come across individuals with extreme late-onset GGE in our clinical practice. We performed a single-center retrospective cohort study

to provide a detailed electro-clinical, management, and prognostic profile of individuals ≥50 years of age (older adults and the elderly) with de novo, extreme-late onset GGE. Additionally, we performed a systematic review of the literature to supplement the data from our cohort.

2 | METHODS

After institutional review board approval, a single-center, retrospective cohort study was performed. We used the prospectively maintained EEG database to identify patients fulfilling the following criteria: (a) ≥50 years of age at the time of EEG; (b) underwent outpatient laboratory EEG or an epilepsy monitoring unit (EMU) evaluation between January 01, 2015 and December 30, 2019; (c) EEG findings consistent with generalized epilepsy. The electronic medical records (EMR) of these patients were reviewed. The study population was identified after excluding the following patients: (a) seizure onset <50 years of age; (b) GGE history in remission with late relapse; (c) history of developmental delays; (d) history of perinatal injury or cortical abnormalities on MRI that could contribute to the electro-clinical presentation (e) patients with dementia; (f) anoxic brain injury (g) metabolic derangements at the time of EEG.

This was followed by detailed extraction of the EEG findings, seizure-related data, family history, seizure triggers (sleep deprivation, photosensitivity, alcohol use), and history of status epilepticus, management, and seizure outcomes at the last follow-up. Seizure freedom was classified as no seizures for ≥1 year at the last follow-up. The inter-ictal EEG findings were classified based on standardized guidelines.[7] Of note, all patients undergo hyperventilation and photic stimulation at our institution. Anti-seizure medications (ASMs) were classified as current ASMs (on the last follow-up) vs historical (not being used at the last follow-up) for each patient.

We used medians and quartiles (interquartile range (IQR = first–third quartiles)) or mean and standard deviation (SD) for continuous variables, depending on the distribution.

2.1 | Literature review

We performed a systematic literature review of late-onset GGE following the guidelines set forth by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[8] on PubMed using the following search strategy: ((idiopathic generalized epilepsy) OR (genetic generalized epilepsy)) AND (((late-onset) OR (adult*)) OR (elderly)) with filters: from January 1, 1973 to December 21, 2022, Humans, and English was used. The search period ended on August 18, 2022. The titles and abstracts of all the articles were reviewed, and full-length articles of relevant articles were retrieved. The references of these articles were reviewed to include other relevant articles that were initially missed. Only manuscripts that provided details on individual patients with GGE onset after 50 years were included.

3 | RESULTS

A total of 152 older adults and elderly patients had EEG findings consistent with generalized epilepsy during the 5-year study period. Twelve (7.9%) patients fulfilled the study criteria and had de novo GGE onset at ≥50 years of age (extreme late-onset GGE). EMR documented the absence of seizures during younger years in these patients, which included 9 (75%) females. The mean age at diagnosis based on EEG findings was 60.9 [SD = 4.9; median = 61 (IQR = 58–65)] years. None of the EEG showed generalized slowing, paroxysmal fast activity or photoparoxysmal response. Seven of these patients underwent EEG monitoring in the EMU and the rest had an outpatient laboratory EEG. Table 1 provides individual-level data.

The median age of seizure onset was 56 (IQR: 52–59). Prior to GGE diagnosis and during the follow-up, 9 of 12 (75%) had a primary generalized tonic–clonic (PGTC) seizure, including five where it was the only seizure type (three additionally had myoclonic seizures and one absence seizures). Three (25%) only had absence seizures. The initial presentation leading to a GGE diagnosis was absence status epilepticus in a 61-year-old patient (Table 1, Patient #1), who presented to the emergency department with acute confusion. She had electro-clinical absence status epilepticus with EEG findings of 3-Hz generalized spike and wave. Her confusion improved after 2 mg of IV lorazepam, followed by another 2 mg, which improved her EEG. She was admitted to the EMU and started on long-term ASM (Zonisamide).

The generalized spike–wave complex was the most common finding. It was seen in 10 (83.3%) patients, followed by generalized polyspikes in 7 (58.3%), and five patients had both. Photoparoxysmal response was seen in 1 patient at 15 and 20 Hz. In three patients, HV-associated activation of the generalized epileptiform discharges was noted. Family history was reported in 5 (41.6%), including three who had first-degree relatives (two sisters and one daughter) with epilepsy. Four (33%) patients reported seizure triggers, including three in the setting of sleep deprivation, and one reported photosensitive seizures.

TABLE 1 Electro-clinical findings of 12 older adults and elderly individuals with extreme late-onset GGE onset

Patient number, sex	Age at diagnosis (years)	Seizure onset (years)	EEG findings	Family history	Seizure types	Total ASMs tried	Historical ASMs	Current ASMs (at last follow-up)	Seizure free (>1 year f/u)
1. F[a]	61.9	56	PSPK, SWC	Yes	Absence	3	2 (PHT, ZNS)	LTG	Yes
2. F	66.5	51	PSPK, SWC	Yes	PGTC, absence	3	1 (PHT)	LTG, LEV	Yes
3. F	68.2	68	SWC	No	PGTC	3	1 (PHT)	LEV, LTG, CLZ	Yes
4. F	64.9	57	PSPK, SWC	No	PGTC, Myoclonus	3	2 (LEV, LCM)	LEV	Yes
5. M	60.2	60	PSPK	No	PGTC	2	1 (TPM)	VPA	Yes
6. F	65.4	62	SWC	Yes	Absence	1	0	LEV	Yes
7. F	62.6	57	SWC	No	PGTC	2	0	LEV, CLZ, VPA	Yes
8. M	54.2	51	SWC	No	PGTC	2	0	ZNS, LEV	Yes
9. F[b]	55	54	SWC	Yes	Myoclonus, PGTC	1	0	LEV	No
10. F	58	50	PSPK, SWC	No	PGTC, myoclonus	1	0	LTG	Yes
11. M	60	59	PSPK	No	Absence	2	0	LEV, CLB, CLZ	Yes
12. F	52	52	PSPK, SWC	Yes	PGTC	1	0	LEV	Yes

Abbreviations: ASMs = Anti-seizure medications, CLB = Clobazam, CLZ = Clonazepam, LEV = Levetiracetam, LTG = Lamotrigine, PGTC = Primary Generalized Tonic Clonic, PHT = Phenytoin, PSPK = polyspike, SWC = Spike and wave complex, VPA = Valproate, ZNS = Zonisamide.

[a]Initial presentation with absence status epilepticus.

[b]Diagnosed with MERRF.

All patients had a clinical follow-up of more than 1 year. Eleven (91.6%) were seizure-free for at least 1 year at the last follow-up. At the last follow-up, the only patient with continued myoclonic seizures (Table 1, patient #9) was diagnosed with a mild variant of myoclonic epilepsy with ragged red fibers (MERRF). She had myoclonic seizure onset at the age of 54 years and was diagnosed a year later after a PGTC. She underwent genetic testing after her son was diagnosed with MERRF and was found to have 8344A>G pathogenic variant in the mitochondrial gene MT-TK. One patient passed away for non-seizure-related reasons. Patients had tried a median of 2 (IQR = 1–3) ASMs, including four patients who were seizure-free after monotherapy trial (Table 1). Levetiracetam was the most common anti-seizure medication used in this cohort (n = 9), followed by Lamotrigine (n = 3) and Valproic acid (n = 2).

3.1 | Literature review

The literature search revealed 817 articles (PRISMA Flowchart; Figure S1). After reviewing the titles, abstracts, and subsequent full-length articles, as appropriate, six articles providing details on 10 patients were included in the literature review. Table 2 provides details on the electroclinical findings of these 10 patients.

4 | DISCUSSION

All late-onset epilepsies should be considered focal in origin,[9] until proven otherwise. The "otherwise" scenario to this maxim can occur in the form of extreme late-onset GGE in older adults and the elderly. It accounted for approximately 1 in 12 (7.9%) individuals with generalized epilepsy in this age group in our study. Our cohort of 12 patients is larger than the combined reported literature. Given the clinical and prognostic importance of epilepsy-type characterization, it is essential to consider various aspects of extreme late-onset GGE in older adults and the elderly.

4.1 | Demographics

The extreme late-onset GGE manifested as late as the 68th year of life in our cohort. In the literature, we came across six individuals who had seizure onset in their seventies, with the oldest reported individual at the age of 80 years. After combining our cohort with the cases reported in the literature (combined cohort), nearly two-third (14 of 22) of patients with extremely late-onset GGE are females. Nearly half (10 of 22) patients in the combined cohort had a family history of epilepsy, substantially higher than 13% of first- and second-degree relatives with epilepsy among the typical GGE population.[10] Therefore, family epilepsy history, which often serves as a diagnostic clue to GGE in younger patients, may be an even stronger indicator of late-onset GGE, especially when it is a non-symptomatic epilepsy in the family member.

4.2 | Seizure types and EEG findings

PGTC was the most common seizure type, noted in more than three-fourths (18 of 22) of the combined cohort. Absence seizures can be confused with encephalopathy or frank dementia in this age group. Four patients (one in our cohort and three in the literature) whose initial presentation leading to GGE diagnosis was in the form of acute confusional state secondary to absence status epilepticus diagnosed on EEG monitoring. The possibility of brief absence seizures being missed until the patient went into a status cannot be ruled out. Symptomatic de novo absence status, especially after benzodiazepine withdrawal, may occur in older adults and the elderly.[11,12] There are also reports of a late relapse of GGE presenting as absence status in later years.[13,14] In contrast, we report extreme late-onset GGE presenting exclusively with absence seizure, including somewhere the initial presentation is in the form of absence status.

Given that GGE is not the "default" clinical diagnosis in older adults and the elderly, EEG is a critical diagnostic tool. While the median age of seizure onset in our cohort was 56 years, the correct diagnosis was only made at a median age of almost 61 years, when EEG findings consistent with GGE, mainly in the form of generalized spike and waves or polyspikes, were noted.

4.3 | Outcomes

Most patients (11 of 12) were seizure-free for more than a year at the last follow-up, suggesting a good prognosis of extreme late-onset GGE, especially given that one-third of patients only required ASM monotherapy. Of note, the good prognosis in this cohort was achieved using newer-generation ASMs, and only two patients were on Valproate at the last follow-up. It is clinically relevant as the pharmacokinetics of valproate are complex in the elderly population.[15] Patients reported in literature also had good seizure outcomes, but in contrast to our cohort, 6 of 10 were on valproate.

The re-emergence of seizures after a prolonged period of remission in patients with GGE is a known

TABLE 2 Literature review of individuals with de novo GGE after the age of 50 years

Author	Patients included	Seizure onset (years; sex)	Presenting symptom	Family history	EEG findings	Seizure types	PPR	Diagnosis	Outcomes
Brigo et al	n = 1*	64 (F)	GTC, Acute confusional state	No	Generalized 3 Hz SWC + PSPK	GTC Absence	No	ASE	Seizure free on VPA
Tóth et al	n = 2	72 (M)	GTC	Yes	Generalized spike–wave	GTC Myoclonus	NR	JME	Seizure free on VPA
		76 (F)	GTC Myoclonus	Yes	Generalized SWC	GTC Myoclonus	NR	JME	Seizure free on VPA
Pro S et al	n = 1	72 (F)	Acute confusional state	No	Generalized 3 Hz SWC, PSPK	Absence	Yes at 18 Hz	ASE	LTG and was seizure free till reduced meds
Terzano et al	n = 1^	70 (F)	Acute confusional state, Myoclonus	No	Generalized SWC, PSPK	GTC, myoclonus	Yes at 10–25 Hz	"Petit mal status"	NA
Michel et al	n = 2	80 (M)	NA	Yes	Generalized 3–3.5 Hz SWC, PSPK	GTC	NR	EGTCS	LTG, "Good control"
		74 (F)	NA	Yes	Generalized 4 Hz SWC, PSPK	GTC	NR	EGTCS	VPA, "Good control"
Marini C J et al.	n = 3	75 (F)	Myoclonus, GTC	No	Generalized 3–5 Hz SWC, PSPK	Myoclonus, GTC	NR	"Adult-onset myoclonic epilepsy"	Seizure free on VPA
		50 (M)	Myoclonus, GTC	No	Generalized SWC, PSPK	Myoclonus, GTC	NR	"Adult-onset tonic–clonic epilepsy"	Clonazepam, seizure free
		69 (M)	GTC	Yes	Generalized 4–5 Hz spike–wave, and polyspike	GTC	NR	"Adult-onset tonic–clonic epilepsy"	Seizure free on VPA

Note: Electro-clinical/electrographic improvement with *4 mg lorazepam and ^10 mg diazepam.

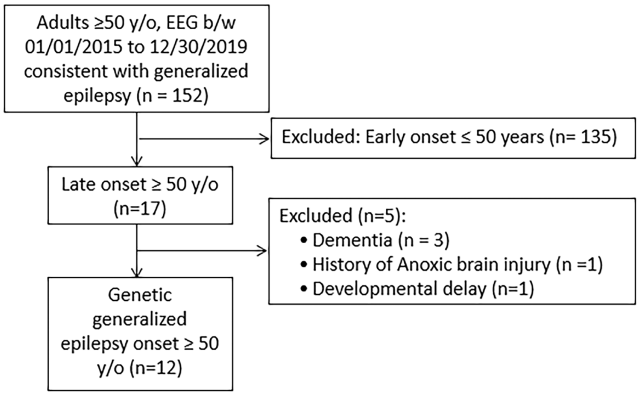

FIGURE 1 Study population

phenomenon.[4,16,17] This late relapse is thought to be triggered by an acquired factor, which enhances the genetic epileptogenic tendency.[17] Similarly, it is likely that the late pathophysiological changes, either neurodegenerative or vascular, in the setting of certain triggers like sleep deprivation (trigger for three patients) can "unmask" the underlying genetic predilection to seizures late in life. Furthermore, unlike children and adolescents with GGE, the underlying genetic etiology in this cohort seems relatively benign given that it is insufficient for independent expression as seizure, which likely contributes to an overall favorable seizure prognosis.

Our study is limited by retrospective design. We only included patients where individuals explicitly denied ever having any seizure types in the past. However, the possibility of recall bias cannot be ruled out. We present data on 12 patients on this rare entity, which is inadequate to draw a definitive conclusion about extreme late-onset GGE. We performed a thorough systematic review of the literature to supplement our cohort and have presented the most comprehensive possible picture of this GGE population. The study design does not allow assessing extreme late-onset GGE incidence in older adults and the elderly with new-onset epilepsy. It is a critical epidemiological and clinical question requiring future research (Figure 1).

5 | CONCLUSION

We present a cohort of 12 patients with extreme late-onset GGE (≥50 years of age). Although relatively rare, this form of GGE challenges the dogma of late-onset epilepsy being focal in origin. We found that close to half of these individuals have a family history of epilepsy. Absence seizures may be the only seizure type in a few patients. A vast majority respond well to ASM therapy, highlighting the need for correct epilepsy-type diagnosis.

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DISCLOSURES

No relevant disclosures. Drs. Alzahrany, Punia report no disclosures.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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