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High rates of early remission pattern in adult-onset compared with earlier-onset idiopathic generalized epilepsy: A long-term follow-up study

Emanuele Cerulli Irelli [a], Biagio Orlando [a], Enrico M Salamone [a], Giacomo Fisco [a], Francesca A Barone [a], Alessandra Morano [a], Martina Fanella [a], Jinane Fattouch [a], Mario Manfredi [a], Anna T Giallonardo [a], Carlo Di Bonaventura [a,*]

[a] Epilepsy Unit, Department of Human Neurosciences, Policlinico "Umberto I", "Sapienza" University, Rome, Italy

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ABSTRACT

Objective: To investigate electroclinical characteristics and prognostic patterns of adult-onset vs. younger-onset idiopathic generalized epilepsy (IGE) patients during long-term follow-up.

Methods: In this single-center retrospective cohort comparative study, adult-onset IGE was defined as onset after 20 years of age. Patients with a follow-up duration between 10 and 30 years from epilepsy diagnosis were enrolled. Maximum follow-up duration was limited to 30 years to ensure a better comparison of prognostic data between adult-onset and younger-onset patients. The Benjamini-Hochberg false discovery rate (FDR) method was applied to obtain FDR-adjusted p-values.

Results: A total of 177 IGE patients were recruited and 27 adult-onset IGE patients were identified (15.3%). Follow-up duration was similar between younger- and adult-onset IGE patients and 74% of subjects performed at least one 24-hour EEG recording. Of adult-onset IGE patients, 8/27 were diagnosed with juvenile myoclonic epilepsy, while 19/27 were diagnosed with generalized tonic-clonic seizures (GTCS) only. EEG photosensitivity and absence seizures were significantly less frequent among adult-onset IGE patients as compared with younger subjects. When considering prognostic patterns, an early remission pattern was significantly higher among adult-onset IGE patients as compared with younger-onset IGE patients (55.6% vs. 24%, adjusted p value = 0.007). Antiseizure medication withdrawal was attempted in 3/27 adult-onset patients, and all had GTCS relapses.

Conclusion: Our study contributes to better defining the electroclinical characteristics and long-term follow-up of adult-onset IGE patients. A favorable long-term seizure outcome was found in adult-onset IGE patients, as evidenced by the high rates of early remission pattern when compared with younger onset patients.

Introduction

Idiopathic generalized epilepsy (IGE) is a common form of epilepsy accounting for almost 20% of patients attending epilepsy outpatient clinics [1]. Four distinct IGE syndromes have been recognized by the International League Against Epilepsy (ILAE). These syndromes present with consistent clinical overlap and share genetic causative factors, suggesting a common pathophysiological background [2].

Seizures in IGE typically start during childhood or adolescence, but late-onset forms have been described in a minority of patients [3]. The existence of adult-onset IGE has been questioned by many authors considering that a remarkable proportion of patients with adult-onset GTCS and an electroclinical diagnosis of IGE may have experienced myoclonia and/or absences during childhood and adolescence, which were unnoticed until a careful reassessment of their clinical history [4]. Conversely, patients with late-onset GTCS can frequently be misdiagnosed with focal epilepsy due to the uncommon presentation of IGE during adult life, and inappropriate antiseizure medications (ASMs) could be prescribed, possibly affecting prognosis and quality of life [5].

Although some authors have previously explored the electroclinical characteristics of adult-onset IGE, considerably fewer electroclinical differences have been described in these patients than in patients with a more classical age of onset [3,6,7]. When considering seizure outcome, data regarding adult-onset IGE are relatively scant since the majority of existing studies did not investigate appropriately this topic. Cutting et al. described a relatively benign prognosis in their cohort by investigating

* Corresponding author.
E-mail address: c_dibonaventura@yahoo.it (C. Di Bonaventura).

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seizure outcome during the last year of follow-up [7]. However, long-term follow-up data and prognostic patterns addressing dynamically seizure control in this IGE subgroup are still missing.

In this paper, we aimed to investigate electroclinical characteristics and prognostic patterns of adult-onset IGE patients (age of onset >20 years) during long-term follow-up (≥10 years) as compared with IGE patients with a younger age of onset.

Methods

This retrospective cohort comparative study was conducted according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines at the epilepsy outpatient clinic of Sapienza University of Rome and was approved by the local ethics committee. Data from patients followed from 1990 to 2020 were retrospectively reviewed.

The diagnosis of IGE was made by two trained epileptologists (ECI, ATG) according to the following criteria [8]: history of at least one generalized seizure (generalized tonic-clonic seizure, absence seizure, myoclonic seizure); generalized spike-and-wave discharges/generalized polyspike-and-wave discharges equal to 3 Hz or between 3 and 6 Hz in at least one EEG exam; normal brain MRI/CT scan (except for minor changes such as arachnoid cysts etc.). A diagnosis of IGE was excluded in case of focal seizures, major abnormalities on brain MRI and CT (potentially epileptogenic), cognitive deficit other than mild intellectual disability and/or borderline intellectual functioning and clinical suspicion of an underlying epileptic encephalopathy.

The inclusion criteria for this study were the following: 1) a diagnosis of IGE, according to criteria defined above; 2) availability of an adequate medical documentation, including at least 1 standard EEG recorded in our lab and exhaustive information on seizure outcome and semiology; and 3) a follow-up duration between 10 and 30 years starting from epilepsy diagnosis.

Patients with an age of onset >20 years were considered to have adult-onset IGE [6,9] and were compared with patients with an age of seizure onset ≤20 years. Maximum follow-up duration was limited to 30 years in order to ensure a more reliable comparison of prognostic data between adult-onset and younger-onset patients. Adult-onset IGE patients were excluded if there was any doubt regarding the occurrence of minor seizures (i.e., absence or myoclonic seizures) prior to 20 years of age.

Clinical and EEG data were reviewed by two trained epileptologists and the IGE syndromes defined by the latest ILAE classification, including the latest task force proposal recently published on the ILAE website, were considered for analysis [10,11]. Follow-up data on seizure type(s), frequency, and ASMs were collected by reviewing the clinical charts for each visit.

The following prognostic categories were assessed in all patients according to criteria previously defined by Beghi et al.: early remission (1+ years of seizure freedom starting within 2 years after diagnosis and persisting for the entire duration of the follow-up), late remission (1+ years of seizure freedom starting 2 or more years after diagnosis and persisting for the entire follow-up), relapsing-remitting course (2+ periods of seizure freedom lasting 1+ years with intermediate relapses), worsening course (1+ years of seizure freedom followed by a relapse without subsequent remission), and no remission (no periods of seizure freedom lasting 1+ years during the entire follow-up) [12].

The main outcome of our study was to evaluate electroclinical characteristics and prognostic patterns of adult-onset IGE patients compared with patients with a younger age of onset.

Statistical analysis

Data were tested for normal distribution using Shapiro-Wilk test and data visualization methods. Data were presented as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. Comparisons across relevant groups (adult-onset IGE vs. younger-onset IGE) were performed with student t-test or Mann-Whitney U test in cases of normal or non-normal distribution, respectively. Categorical variables were presented as frequencies (counts) and compared across relevant groups (adult-onset IGE vs. younger-onset IGE) using the Fisher exact test or chi-square test. All p values were adjusted using the Benjamini-Hochberg false discovery rate method, and adjusted p values < 0.05 were considered as statistically significant [13,14].

Results

Of 450 patients with a confirmed diagnosis of IGE, 177 subjects were included according to study methods (Supplementary figure, S1). Median age of the patient population was 30 years (IQR 25–36.5), and median follow-up was 17 years (IQR 11.5–23). Median age of onset was 14 years (IQR 10–17) and adult-onset IGE was identified in 27/177 subjects (15.3%). Follow-up duration did not differ between adult-onset and younger-onset IGE patients (Table 1). The last follow-up visit was performed either during 2020 or 2021 in 151/177 subjects (85.3%), and no patient ended follow-up before 2014.

Among adult-onset IGE patients, 8/27 (29.6%) were diagnosed with juvenile myoclonic epilepsy (JME) and 19/27 (70.4%) with IGE with

Table 1
Electroclinical characteristics of the patient population according to age of epilepsy onset.

	Adult-onset IGE (27 pts)	Younger-onset IGE (150 pts)	Adjusted *p* values
Age, years, median (IQR)	40.6 (39–47)	29 (24–35)	<0.001*
Sex, female, n (%)	16 (59.3)	89 (59.3)	1
Follow-up duration, years, median (IQR)	14 (11–25)	17 (11–23)	0.62
Age of epilepsy onset, median (IQR)	24 (22–26)	13 (9–15)	<0.001*
Family history of epilepsy in 1st or 2nd relative, n (%)	7 (25.9)	66 (44)	0.16
History of febrile seizures, n (%)	2 (7.4)	15 (10)	1
Cognitive abnormalities, n (%)	0	17 (11.3)	0.16
Psychiatric comorbidity, n (%)	4 (14.8)	25 (16.7)	1
Seizure types experienced, n (%)			
Absence seizures	2 (7.4)	83 (60.1)	<0.001*
Myoclonic seizures	8 (29.6)	76 (50.7)	0.13
Generalized tonic-clonic seizures	26 (96.3)	115 (83.3)	0.31
Epilepsy syndrome			
Childhood absence epilepsy, n (%)	0	14 (9.3)	0.31
Juvenile absence epilepsy, n (%)	0	25 (16.7)	0.03*
Juvenile myoclonic epilepsy, n (%)	8 (29.6)	76 (50.7)	0.13
Eyelid myoclonia with absences, n (%)	0	8 (5.3)	0.71
IGE with generalized tonic-clonic seizures alone, n (%)	19 (70.4)	31 (20.7)	<0.001*
Main pharmacological data			
ASMs at last observation, median (IQR), n	1 (1–2)	1(1–2)	0.6
Valproate used during follow-up, n (%)	15 (55.6)	119 (79.3)	0.02*
Monotherapy regimen at last observation, n (%)	19 (70.4%)	93 (62%)	0.62
EEG characteristics			
Photosensitivity, n (%)	3 (11.1)	61 (40.7)	0.01*
Polyspikes on EEG, n (%)	12 (44.4)	93 (62)	0.16
Focal abnormalities, n (%)	4 (14.8)	12 (8)	0.55
Generalized paroxysmal fast activity, n (%)	2 (7.4)	9 (6)	0.8
Eye closure sensitivity, n (%)	1 (3.7)	22 (14.7)	0.43

Abbreviations: ASM= antiseizure medication; IGE= idiopathic generalized epilepsy; IQR = Interquartile Range; * adjusted *p*-value < 0.05.

GTCS alone. A total of 131/177 patients (74%) in the overall cohort, including 21/27 patients (77.8%) with adult-onset IGE, underwent a 24-hour EEG, whereas a routine EEG was available for all patients as for study criteria. The median age at the time of the analyzed routine EEG recording was 25 years (IQR 23–26) in adult-onset subjects and 16 years (IQR 11–18) in the younger-onset IGE subgroup, with no significant differences in terms of delay from epilepsy onset to analyzed EEG recording between the two age groups (adjusted p-value, 0.85). A treatment-naïve routine EEG was available in 19/27 (70.4%) adult-onset IGE patients and in 81/150 (54%) younger-onset subjects (adjusted p value, 0.30). Generalized epileptiform discharges (either spike-wave discharges and/or polyspike-wave discharges) were found in at least one EEG in all included patients. Photosensitivity was significantly less frequent among adult-onset IGE patients as compared with IGE patients with a younger age of onset (11.1% vs. 40.7%, adjusted p value =0.01), whereas these groups did not statistically differ with respect to other EEG findings, including the occurrence of generalized paroxysmal fast activity (GPFA) during sleep. A detailed comparison of electroclinical characteristics between adult-onset and younger-onset IGE patients is summarized in Table 1. The main electroclinical differences between the two groups are illustrated in Fig. 1.

The most common fist-line ASM was Valproate (VPA) in 106/177 patients, followed by Levetiracetam (LEV) in 35 (19.8%) and Lamotrigine (LTG) in 15 (8.5%). The mean number of ASMs tried during clinical history was lower in adult-onset IGE patients compared with younger-onset IGE patients (1.8 SD ±1 vs. 2.4 SD ±1.4, adjusted *p* value = 0.09), whereas a monotherapy regimen at the last observation (adult-onset: 19/27 −70.4%- vs. younger-onset: 93/150 −62%-, adjusted p value=0.6) and the mean number of ASMs at last observation (adult-onset: 1.3 SD ±0.5 vs. younger-onset: SD 1.45±0.7, adjusted *p* value = 0.6) were similar between the two groups. At the last follow-up visit, the most common ASM was VPA in 92/177 (52%) patients, followed by LEV in 69 (40%), LTG in 37 (20.9%), Topiramate in 12 (6.8%) and Perampanel in 10 (5.6%). VPA use at the last follow-up visit was lower in adult-onset patients as compared with younger-onset subjects (11/27 −40.7%- vs 81/150 −54%-, adjusted *p* value = 0.43), as opposed to LEV use, which was more common in late-onset patients (16/27 −59.3%- vs 53/150 −35.3%-, adjusted p value=0.08). ASM withdrawal was attempted in 3/27 adult-onset IGE patients, and all had GTCS relapse. Among younger-onset IGE patients, ASM withdrawal was attempted in 36/150 patients, and seizure relapse was experienced in 31/36 (84.8%). Median disease duration at the moment of ASM withdrawal was 5 years (IQR 3–7) in adult-onset patients and 6 years (IQR 4–10) in younger-onset patients (adjusted *p* value=0.6).

As regards prognostic patterns, an early remission pattern was significantly higher among adult-onset vs. younger-onset IGE patients (15/27 −55.6%- vs. 36/150 −24%-, adjusted *p* value = 0.007). A detailed description of prognostic pattern distribution according to age of onset is illustrated in Fig. 2.

Discussion

Our study contributes to better define the electroclinical features of adult-onset IGE and provides long-term follow-up data in this IGE subgroup.

An extraordinarily high rate of early remission pattern was observed in adult-onset IGE, as almost half of these patients achieved a sustained remission until the end of follow-up within 2 years of the first ASM prescription. This finding appears to be surprising if compared with the proportion of patients presenting early remission pattern in the overall IGE population that, according to previously published studies, amounts to almost 25% of the cases [15].

Our data regarding the excellent medication response of adult-onset IGE patients appears to be in line with previous observations [7,9], although long-term follow-up data and prognostic patterns have never been previously investigated. The observed discrepancy in terms of long-term seizure outcome between the two IGE subgroups could be partially explained by the striking lower rate of absence seizures and the lower number of seizure types among adult-onset IGE as compared with younger onset patients, which are well-known prognostic factors in IGE [16,17]. Despite the high proportion of adult-onset patients experiencing early remission in our cohort, we always observed the occurrence of GCTS relapse in those patients in which the ASM withdrawal was attempted. This latter evidence, to be considered little more than an anecdotal observation (indeed drug withdrawal was attempted in only 3 patients), suggested that adult-onset IGE may represent a pharmacodependent IGE subtype with an excellent and early response to medication. Interestingly, though we observed a high rate of early-remission in adult-onset patients, we found that ASM withdrawal attempt was more common in younger-onset patients (24% vs 11.1%). This apparently contradictory finding may be explained by the more active lifestyle of adult-onset patients (involving driving, parenthood, working issues,

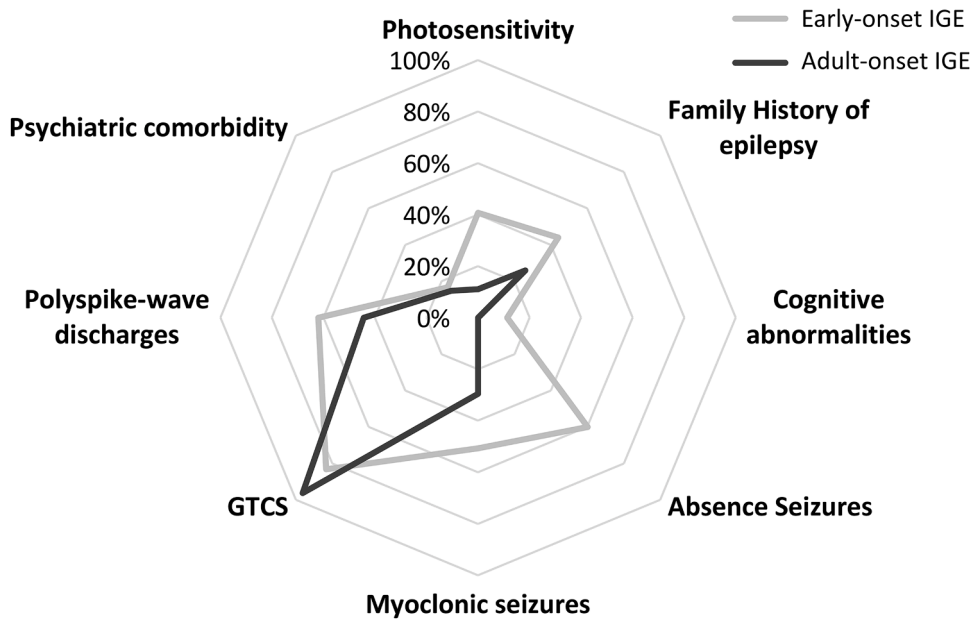

Fig. 1. Radar plot showing main electroclinical characteristics according to age of epilepsy onset.

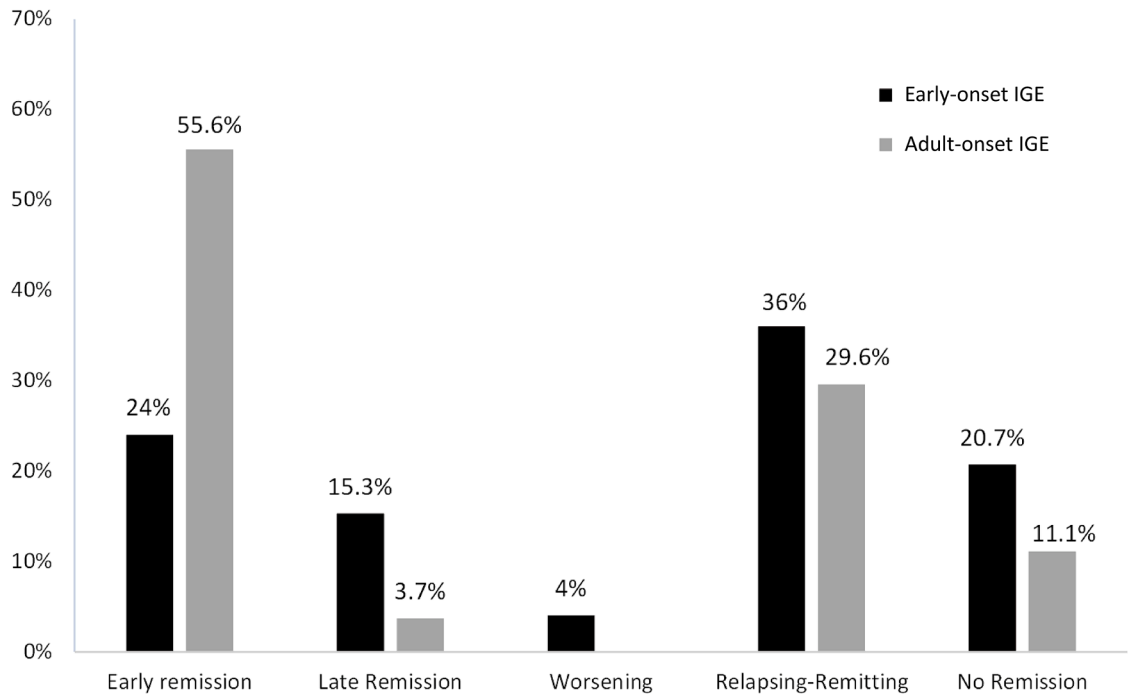

Fig. 2. Prognostic pattern distribution according to age of epilepsy onset, The percentage of patients showing each prognostic pattern is reported above the bars.

etc.) which may lead both patients and clinicians to be particularly concerned about medication withdrawal.

In addition to the prognostic profiles of adult-onset IGE, our study revealed some interesting new electroclinical findings in adult-onset IGE patients. Indeed, the large use of 24-hour EEG in our cohort allowed us to increase the diagnostic accuracy of adult-onset IGE and investigate the EEG findings during sleep in these patients. Surprisingly, we found a similar occurrence of generalized fast activities during sleep between younger- and later-onset subjects. Although previous reports had considered GPFA as distinctive of early-onset IGE persisting into adult life [18], no authors had specifically focused on this peculiar EEG pattern in late-onset patients. Moreover, the early- and late-onset groups did not differ in terms of presence and characteristics of the other spontaneous epileptiform abnormalities (including generalized discharges and focal spikes), further supporting the concept of a biological continuum between younger- and later-onset IGE forms [3,9]. In the context of EEG findings, our study documented a low rate of EEG photosensitivity in late-onset patients. The different occurrence of photosensitivity in early and late-onset IGE appears to be a debated topic since previous studies have reported contrasting results [9,19]. However the well-known age-dependent mechanism of EEG photosensitivity in idiopathic epilepsies seems to support our observation [20]. Finally, we confirmed IGE-GTCS alone and JME as the most common syndromes in adult-onset IGE patients [9], in whom we also detected a lower rate of absence seizures, as previously highlighted by previous studies [3,7].

The main limitations of our study were: 1) its retrospective design, which may have resulted in selection bias, recall bias and more generally in information bias. The variable follow-up duration among recruited subjects may also have influenced outcome assessment; 2) the study design including patients with follow-up duration longer than 10 years may have determined an over-representation of IGE persisting in adult life in the younger-onset group, as testified by the high rates of JME, polyspike discharges, photosensitivity and myoclonic seizures in these patients; 3) the hospital-based design, determining an over-representation of more refractory case and possibly reducing the generalizability of our findings [21,22]; and 4) the possible inclusion of pseudo-refractory cases, considering that patient recruitment was not specifically adjusted for this confounding variable.

In conclusion, our study provides new evidence regarding the long-term follow-up data of adult-onset IGE patients. An excellent and early medication response was observed in the majority of patients, though treatment withdrawal may be associated with a high rate of seizure relapse. Finally, our findings further support the concept of a biological continuum of early and late-onset subtypes in the IGE spectrum.

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.

Disclosures

None of the authors have any conflicts of interest to disclose.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.11.019.

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