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Idiopathic Generalised Epilepsy of Late Onset – A separate nosologic entity?

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ABSTRACT

PURPOSE: Seizure onset in idiopathic generalised epilepsies (IGE) is considered to be rare after the second decade of life. We aimed to explore age of seizure onset in patients with IGE and compare “classical” onset to late onset cases.

METHODS: Patients with IGE, treated at the outpatient epilepsy clinic (Medical University of Innsbruck, Austria, 1985-2006, n=798) were retrospectively screened. Inclusion criteria were: Diagnosis of IGE, more than two follow up (FU) visits, duration of FU more than one year, normal brain imaging. We analysed demographic data, age of seizure onset, seizure types, syndromes, neuroimaging and EEG findings, seizure triggers, seizure freedom for one and five years at last FU.

RESULTS: A total of 492 patients (mean age at seizure onset 14.6 years, range 0.1-55, SD 7.9) with IGE were identified: CAE (n=113, range 1-55, SD6.5), JAE (n=75, range 4-39, SD 5.1), JME (n=112, range 2-39, SD 5.7), and EGMA (n=192 range 1-52, SD 17.3). Population was stratified into three groups: 28 patients with seizure onset at >30yrs, 180 between 15 and 30 years and 284 <15years. Distribution of seizure types and epilepsy syndromes differed significantly in group comparison ($p<0.001$); seizure outcome and other clinical variables did not differ throughout the groups.

CONCLUSION: Apart from age related onset of seizure types and syndromes with a loose upper limit of onset age patients with a late onset did not differ from their younger counterparts. Our data does not support the view of IGE of late onset as a separate syndrome.

INTRODUCTION

Idiopathic generalised epilepsies (IGE) account for approximately 15-20% of all epilepsy cases.[1] IGE classification is based mainly on clinical and EEG features. Aside from a genetic predisposition, no other etiology is known.[2] IGE can be divided into eight age related epilepsy syndromes according to the still valid classification of the International League Against Epilepsy (ILAE).[2] Four of these syndromes occur after the neonatal period: Childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with grand mal seizures on awakening (EGMA). Age at onset and seizure types are taxonomic criteria: According to the ILAE classification CAE-patients usually have their seizure onset between the age of 6 and 7 years, JAE and JME - during puberty and EGMA - during the second decade of life. [2, 3]

A considerable number of patients may not fulfil these criteria related to the limits of seizure onset age. IGE cases with a later than usual onset have been described.[4-11] In these studies, late onset groups were defined arbitrarily and some authors set the age limit at 20, others at 16 or 18 years.[4, 8-11] It has been suggested, that IGE with late onset shares common biologic determinants with IGE while etiologic factors and relations between each IGE syndrome are not clearly understood and discussed controversially.[4, 9, 11]

Therefore, we aimed to study a large population with IGE in a single centre for determining the age range at disease onset and comparing clinical features of late onset patients with those who had classical age at onset.

METHODS

We identified 798 patients with IGE in the database of the epilepsy unit at the Department of Neurology, Medical University of Innsbruck, Austria. IGE was defined according to the ILAE classification (Commission on Classification, 1989). Inclusion criteria for the study sample were: Diagnosis of IGE, more than two follow up visits at our

department (at least one visit after 1985), duration of follow up period more than one year, normal brain imaging, no late de-novo absence status and no signs of focal epilepsy.[2, 12, 13] Three hundred and six patients were excluded due to the following reasons: Less than two follow up visits (n=130), patient files could not be retrieved (n=43), last patient visit before 1985 (n=54), follow up period of less than 1 year (n=15) focal or cryptogenic epilepsy additional to IGE (n=5), brain trauma (n=14), meningitis (n=4). In addition, 41 patients with uncertain diagnosis were excluded.

All patients had EEG and neuroimaging (CT or MRI). Patient charts included a detailed medical history.

We analysed biographic data, especially age at seizure onset and date of the first and the last follow-up. Patients' case histories were screened for seizure types (myoclonic seizures, generalised tonic-clonic seizures and absence seizures at the onset and during the course of epilepsy) and status epilepticus. Syndromes were diagnosed according to the ILAE criteria. Patients with evolving syndromes, for example CAE with late onset who first had absences and later on developed generalised tonic clonic seizures were classified as CAE . Patients with absences in childhood and later myoclonic jerks with or without grand mal seizures on awakening were classified as JME [14]. We analysed family history (first degree relatives with epilepsy), history of febrile seizures, EEG characteristics, neurological and psychiatric findings, compliance, social status, anti-epileptic drug (AED) treatment at the last follow up visit and neuroimaging data. Alcohol, sleep deprivation and stress were regarded as seizure triggers.

As not all original EEGs were retrievable over the long observation period, we extracted the most characteristic records and rated the following EEG phenomena: Generalised spikes and sharp waves, localised spikes and sharp waves, diffuse slowing and local slowing and absence status epilepticus.

Psychiatric comorbidities and cognitive disturbances were categorised as “behavioural disorder/affective disturbance”, “psychosis” and “learning disabled”. Social status was grouped into “independent (from assistance)”, “partially dependent”, “dependent” and “not identified”. Compliance ranged from non-compliance to good compliance.

Seizure outcome was qualified as (i) seizure freedom for more than one year at the last follow up (ii) seizure freedom on their initial AED-treatment (immediate responders) and (iii) patients in terminal remission (seizure freedom for more than 5 years).

Data were processed with MS Excel 2003 and SPSS 14.0. χ^2 test was applied for group comparisons (significance level 0.05). Bonferroni-Holm correction was used as multiple testing was performed (α level given in tables, α_1 - α_{20}). Spearman Rank Order was used for correlation of onset age with the variables.

RESULTS

Four-hundred and ninety-two patients (299 women, 193 men, significantly more women than men – $p < 0.001$) met the inclusion criteria. Age at seizure onset varied from one to 55 years of age (mean - 15 years). Even 80/492 (16.3%) patients had their onset after the age of 20 years. The mean period of ongoing seizure activity was 11 years ranging from less than one year up to 63 years.

One hundred and ninety-two patients had EGMA (39%; age at seizure onset - 0.1 – 51.7 years, mean 17.6, SD 8.7), 112 patients had JAE (22.8%; age at seizure onset - 3 – 39 years, mean 15.6, SD 5.6), 75 patients had JME (15.2%; age at seizure onset - 4 – 39 years, mean 14.3, SD 5.1) and 113 patients had CAE (23%; age at seizure onset - 0.3 – 55 years, mean 9, SD 7.5).

The ages of seizure onset were normally distributed up to the age of 30 years. According to the age at seizure onset the population was divided into three groups (fig. 1): In group I, seizure onset was between 1-15 years ($n=284$), in group II - between 15 - 30 years

(n=180) and in group III - above 30 years (n=28). The proportion of men and women did not differ significantly throughout the groups (table 1, p=0.203).

Table 1 Description of population and comparison of age groups concerning seizure types and syndromes

Groups (age of onset, years)		Total	Group 1 (<15 yrs)	Group 2 (15 – 30yrs.)	Group 3 (> 30yrs.)	p-value
No. of patients		492 (100)	284 (57.7)	180 (36.6)	28 (5.7)	
Median age of onset (yrs.)		13.9	10.25	17.6	35.4	
Gender m	m	193 (39.2)	102 (35.9)	78 (43.3)	13 (46.4)	0.203*
	F	299 (60.8)	182 (64.1)	102 (56.7)	15 (53.6)	
Family history		138 (28)	73 (25.7)	52 (28.9)	13 (46.2)	0.065*
Febrile seizures		21 (4.3)	14 (4.9)	6 (3.3)	1 (3.6)	0.697*
Seizure type(s) at disease onset	GTCS	241 (49.2)	101 (35.6)	117 (65)	24 (85.7)	<0.001
	MS	87 (17.7)	40 (14.1)	45 (25)	2 (7.1)	0.004
	AS	193 (39)	154 (54.2)	34 (18.9%)	4 (14.3)	<0.001
Occurring seizure types	GTCS	461 (93.7)	261 (91.9)	175 (97.2)	25 (89.3)	0.044
	MS	142 (28.9)	75 (26.4)	63 (35)	4 (14.3)	0.027
	AS	259 (52.6)	193 (68)	58 (32.2)	8 (28.6)	<0.001
Syndrome	EGMA	192 (39)	75 (25.7)	96 (53.3)	21 (75)	<0.001
	JME	112 (22.8)	55 (19.4)	54 (30)	3 (10.7)	
	JAE	75 (15.2)	51 (18)	23 (12.8)	1 (3.6)	
	CAE	113 (23)	103 (36.3)	7 (3.9)	3 (10.7)	
Status epilepticus		38 (7.7)	26 (9.2)	8 (4.4)	4 (14.3)	0.073*

Numbers are n(%) unless stated, percentages relate to groups, p-value of group comparison according to χ^2 test,

* α -level after Bonferroni-Holm correction for multiple testing.

GTCS, generalized tonic clonic seizures; MS, myoclonic seizure; AS, absence seizures; EGMA, epilepsy with grand mal on awakening; JME, juvenile myoclonic epilepsy; JAE, juvenile absence epilepsy; CAE, childhood absence epilepsy.

Absences (AS) were the most common seizure type in group I (193/284, 68%, p<0.001, fig. 2) and correlated with an early onset of IGE (p<0.001). The occurrence of

generalised tonic-clonic (GTCS) and myoclonic seizures (MS) in the course of the period with seizure activity differed throughout all groups (see table 1). The age specific distribution of seizure types at disease onset (see fig. 2, table 1) differed in group comparison ($p < 0.001$). GTCS occurred in 93.7% of all patients in the course of the disease, AS in 52.6% and myoclonic seizures in 28.9% (see table 1). At least one episode of status epilepticus occurred in 7.7% of patients (group comparison was n.s., table 1).

The distribution of syndromes (fig. 3) showed significant differences in group comparison ($p < 0.001$): In group I ($n=284$), 75 (26.4%) patients had EGMA, 55 (19.4%) had JME, 51 (18%) JAE and 103 (36.3%) CAE. EGMA was the predominant syndrome in group II (96/180, 53.3%) and group III (21/28, 75%). In group II ($n=180$), 54 patients (30%) had JME, 23 (12.8%) - JAE and 7 (3.9%) - CAE. In group III ($n=28$), three patients (10.7%) had JME, one (3.6%) - JAE and three (10.7%) - CAE (table 1).

Generalised spike and wave or polyspike wave EEG patterns were detected in 84.8% of all patients (417/492). Their occurrence did not differ between the groups. Twenty three patients (4.7%, n.s.) had also localised EEG abnormalities. In 31/492 (6.3%, n.s.) patients, local slowing was seen in EEG, while EEG of 99/492 (20.1%) patients showed diffuse slowing. Only 27/492 (5.5%) patients had normal EEG. In 7/492 (1.4%) patients, EEG documented a non-convulsive status epilepticus.

Family history of epilepsy (table 1) in the first degree relatives was positive in 140/492 (28.5%) patients: In group I - 73/284 (26%), in group II - 63/180 (35%), in group III - 4/28 (14%) patients (group comparison n.s.). The proportion of patients with febrile seizures 21/492 (4.3%) did not show statistically significant results in group comparison (table 1).

Aside from alcohol as a seizure trigger (seizure types and syndromes were not analysed as co-variables in group comparison) no other variable showed a positive correlation (correlation coefficient 0.146, $p=0.001$) with the age at seizure onset (table 2). In patients with seizure onset between 15 – 30 years (group II) 49/180 (27%) patients experienced alcohol

triggered seizures, compared to 43/284 (15%) patients with seizure onset under the age of 15 (group I) (table 2). Seizures were provoked by stress in 51/492 (10.4%, n.s.) patients and by sleep deprivation in 172/492 (35%, n.s.).

Table 2 Comparison of seizure triggers in age-groups

Groups (age of onset, years)	Total	Group 1 (<15 yrs)	Group 2 (15 – 30 yrs.)	Group 3 (> 30yrs.)	p-value
Sleep deprivation	172 (35)	91 (32)	73 (40.6)	8 (28.6)	0.123*
Alcohol	99 (20.1)	43 (15.1)	49 (27.2)	7 (25)	0.005*
Stress	51 (10.4)	28 (9.9)	20 (11.1)	3 (10.7)	0.902*

*Numbers are n(%); p-value of group comparison according to χ^2 test, * α -level after Bonferroni-Holm correction for multiple testing.*

The proportion of patients with psychosocial problems did not differ significantly in group comparison. Behavioural disorders/affective disturbances were observed in 140/492 (28.5%): Mild affective disturbances were noted in 113/492 (23.1%, n.s.) patients, 32/492 (6.5%, n.s.) had learning disabilities and 12/492 (2.4%) had a history of psychosis. Social status was rated as “independent” in the majority of patients 471/492 (95.7%, group comparison n.s.). At the last follow up 15/492 (3%) patients received antidepressants or anxiolytics, while 30/492 (6.1%) patients had a history of treatment with antidepressants or anxiolytics. Compliance was good in 326/492 (66.3%) patients.

Two hundred and ninety eight out of all patients (60.6%) were seizure free and 144/492 (29.3%) were in terminal remission at the last follow-up visit (table 3).

Table 3 Outcome variables in group comparison

Groups (age of onset, years)	Total	Group 1 (<15 yrs)	Group 2 (15 – 30 yrs.)	Group 3 (> 30yrs.)	p-value
Seizure Freedom	298 (60.6)	173 (60.9)	108 (60)	17 (60.7)	0.981*
Remission	144 (29.3)	78 (27.5)	57 (31.7)	9 (32.1)	0.589 *

Seizure freedom on initial treatment	117 (23.8)	56 (19.7)	55 (30.6)	6 (21.4)	0.024*
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*Numbers are n(%); p-value of group comparison according to χ^2 test, * α -level after Bonferroni-Holm correction for multiple testing.*

Sodium valproate (VPA) was the most frequently used AED - 66.1% of patients received VPA at the last follow up. Patients with an initial response to AED significantly ($p < 0.001$) correlated with seizure freedom and remission: 83.8% (98/117) of patients who initially responded to medication were seizure free at the last follow up and 43% (51/117) were in remission.

DISCUSSION

The age of seizure onset in our large group of patients with IGE showed a broad age range - from the first year of life up to 55 years with a normal distribution up to the age of 30. From the fourth decade on, the distribution was skewed with only very few patients ($n=6$) older than 40. Overall only 28/492 (5.7%) of patients had seizure onset after the age of 30 years.

A relatively high proportion of patients with seizure onset after the second decade of life ($n=80$, 16.3%) in our study sample is in line with the ILAE classification.[2] It demonstrates, however, that a late onset is not as rare as it has been stated in previous studies.[6, 15] We found no statistically significant differences related to prognosis, EEG-findings and characteristic clinical features other than seizure types which are in fact the taxonomic criterion for the classification system. Previous studies suggesting that late onset cases share most of characteristic features with IGE based their assumptions on arbitrarily defined cut-off ages which explains most of the differences between the studies. [4-6;8;9;11] Ages of 16, 18 and 20 years were used as cut-off values.[4, 8-11] Therefore, the proportion of patients with so-called late onset IGE varied substantially between 8.5 and 28%.[8, 9]

In the present study, cut-off ages were not defined a priori. They were based on the observation of the distribution of the ages at onset. None of the clinical features except for seizure types differed significantly in group comparison, underlining the concept of age-related occurrence of seizure types in epilepsy syndromes.[3] However, there are several uncertainties: First, “minor seizures” like brief absences may be overlooked and other seizures may be regarded as non-epileptic (myoclonic jerks). Therefore, the true age at seizure onset may not always be easily detected. For example, in the not yet recognized syndrome of de-novo absence status in the elderly, a certain number of patients may have had minor seizures in childhood.[12] Secondly, the predominating seizure type may change over time within the syndromes. For example, absences and MS in JME tend to remit, while GTCS may be persistent for years.[3] Similar observations have been made for the evolution of AS which may be less pronounced in later ages (phantom absences).[10] Hence, the patients’ age has to be taken under consideration (mean age at the last follow-up was 34.5 years) when comparing different groups. In our study, the age at the last follow-up did not differ significantly between the groups. Finally, in many patients additional neuroimaging MRI was performed, since the diagnosis of generalised seizures, especially absence in adults is not always straightforward. Nevertheless, the occurrence of additional generalized seizure types and a characteristic EEG pattern are the most reliable clue to the syndrome diagnosis.

The treatment response to AEDs was favourable in the majority of patients. The numbers of seizure free patients and those in terminal remission were comparable to other studies.[9, 16] The proportion of patients who became seizure free after the initial drug treatment was only 23.8% which is lower than expected.[16] This may reflect a selection bias towards more difficult to treat patients as some of the seizure free patients may have been treated by general neurologists and were lost for follow up at our institution.

In agreement with previous findings, 8.9% of patients had focal abnormalities in the EEG and 14.6% in neurological examination. The presence of focal findings should not

preclude from diagnosing idiopathic generalised epilepsies if all other features are typical. Nevertheless, the concept of “generalised” epilepsies has been challenged.[17]

Psychiatric comorbidity in epilepsies, including IGE, have been repeatedly investigated.[4, 18-20] These studies consistently show that about 30% of patients will experience a psychiatric disturbance at least once in their life time. This is also reflected in our study where 28.5% of patients had affective disturbances rated by the treating physician on clinical grounds and 6.1% received anxiolytics or antidepressants. Despite the possible influence of psychiatric comorbidities on seizure outcome, we were not able to address this issue specifically in this retrospective survey.[4]

Alcohol (consumption and withdrawal) has been discussed as an effective seizure trigger in literature.[21] Differences within the age groups could either result from a psychosocial phenomenon or a confounding mechanism: Due to the age related habits of drinking, one could hypothesize that alcohol might be more common seizure trigger in later years of life. Since patients are instructed to abstain from alcohol consumption at seizure onset, patients aged younger than 15 at seizure onset are less likely to drink at legal ages (and in the course never experience alcohol as a seizure trigger). Other seizure triggers as sleep deprivation and stress do not play a more important role in late onset cases.

The majority of patients (66.1%) were treated with VPA. Although there are yet no Class I studies comparing the efficacy of VPA with other AED in IGE, two large class III studies (SANAD B and KOMET trial) confirmed its good efficacy and tolerability in these syndromes, supporting VPA as the first choice in IGE.[22, 23]

This study bears considerable methodological limitations in being a retrospective study. To achieve better comparability the ILAE criteria of 1989 were applied, even though some patients were diagnosed with IGE earlier and reclassified later. Diagnostic techniques have improved substantially in the past 20 years and the rate of patients who received a straight forward diagnosis has increased. Although this epilepsy centre can be regarded as a

primary care centre for patients with epilepsy (majority of patients are in adolescence and adulthood) a selection biases towards more severe cases cannot be excluded.

CONCLUSION

In this large cohort of patient with IGE, the age of seizure onset had a loose upper limit with 16.3% after the second decade and 5.7% after the third decade of life. Later onset of seizures was associated with differences in seizure types (emphasizing the age related onset) but not regarding other clinical issues. We cannot confirm the assumption that IGE of late onset might be a separate nosologic entity.

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(2) The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in the Journal of Neurology, Neurosurgery & Psychiatry editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence (<http://jnnp.bmjournals.com/misc/ifora/licenceform.shtml>).

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Figure 1 Age at onset, onset to first potential and at-operative age and end age by sex (mean age at initiation about 15 years)

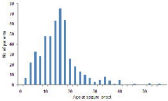


Figure 2 Age spectra (total of cardiac types) in 402 patients with (a) isolated generalized epilepsy (IGE), bilateral tonic-clonus, ITC, repetitive seizures (RTS), generalized tonic-clonic seizures

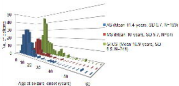


Figure 3 Age-specific onset of syndromes in 402 subjects with sporadic generalized epilepsy (SAG), or focal-onset or cryptogenic GEP (juvenile absence epilepsy; JAE, infantile myoclonic epilepsy; IEME, cryptic with grand mal or absence)

