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ORIGINAL COMMUNICATION

Discontinuing antiepileptic drugs in long-standing idiopathic generalised epilepsy

Bernd J. Vorderwülbecke[1] · Andrea Kirschbaum[1] · Hannah Merkle[1] · Philine Senf[1,2] · Martin Holtkamp[1]

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Abstract

Background Once adults with long-standing idiopathic generalised epilepsy have achieved stable seizure remission, patients or physicians may attempt to discontinue their antiepileptic drug treatment. To date, risk of subsequent seizure relapse across the four idiopathic generalised epilepsy syndromes is largely unknown, and so are the clinical variables associated.

Methods For this retrospective observational study, 256 adult outpatients with idiopathic generalised epilepsy were evaluated. Data were obtained from outpatient charts and, if possible, from additional telephone or mail interviews.

Results In 84 patients (33%), antiepileptic medication was discontinued at least once. Median patient age at antiepileptic drug withdrawal was 33 years, and median duration of subsequent follow-up was 20 years. Seizures recurred in 46% of patients after a median latency of 11 months. Following multivariable analysis, seizure relapse was independently associated with short duration of seizure remission beforehand. If medication was withdrawn after < 5 years of seizure freedom, two-thirds of patients had a seizure relapse, while among those in remission for ≥ 5 years, only one-third relapsed.

Conclusions Discontinuation of antiepileptic drug treatment can be successful in every other adult with long-standing idiopathic generalised epilepsy. Short duration of prior seizure remission appears to be a relevant predictor of seizure recurrence.

Keywords Adults with epilepsy · Generalised genetic epilepsy · Antiepileptic drug withdrawal · Seizure remission · Seizure relapse · Risk factors

Introduction

According to the most recent epilepsy classification of the International League Against Epilepsy, "within the Generalized Epilepsies is the well-recognized and common subgroup of the Idiopathic Generalized Epilepsies (IGEs)". These encompass four distinct syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalised tonic–clonic seizures alone (EGTCS) [1]. In CAE, seizures typically commence at school age and cease during adolescence, but ~ 25% of patients continue to have ongoing seizures during adulthood [2–4]. JAE, JME and EGTCS manifest during adolescence and usually persist for decades [5, 6]. Evidence is growing that antiepileptic drugs (AEDs) may be reduced and finally discontinued in seizure-free patients [7–9]. However, data are lacking on subsequent seizure relapse risk in adults with long-standing IGE across all four syndromes. This retrospective study aimed at identifying risk factors for seizure recurrence after AED discontinuation in a large cohort of adult IGE patients with a median total follow-up of > 40 years.

Methods/patients

As for five previous studies [6, 10–13], an archive was reviewed that contains the charts of 343 outpatients with IGE treated at a tertiary care centre between 1955 and 2012, more than 90% of them by Dieter Janz (1920–2016), one of the first describers of JME. Based on phenotypical features, patients were retrospectively allocated to one of the four IGE syndromes. Subjects with absence seizures (with or without

✉ Bernd J. Vorderwülbecke
bernd.vorderwuelbecke@charite.de

[1] Department of Neurology, Epilepsy-Center Berlin-Brandenburg, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

[2] Department of Psychosomatic Medicine, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

additional generalised tonic–clonic seizures (GTCS)) were diagnosed with absence epilepsy (CAE if seizure onset was before the 11th birthday, and JAE if afterwards) [13, 14]; those with myoclonic seizures (irrespective of other seizure types) with JME; finally, those with GTCS only were diagnosed with EGTCS. Interictal EEG prior to initiation of AEDs was available for a minority of patients only. Thus, diagnosis of IGE and allocation to one of the four epilepsy syndromes were entirely based on clinical grounds.

Data were collected from the outpatient charts and, for patients still alive and within reach, from an additional telephone or mail survey with the patients or their next-of-kin in 2011 or 2012. Only subjects with ≥ 20 years of follow-up, defined as the time between the first recognised seizure and the last patient contact, were further evaluated. Positive family history was defined as evidence of epilepsy in first-degree relatives. If subjects tried to discontinue their AEDs more than once, the last attempt was evaluated. The main outcome parameter was overall seizure recurrence. Since absence or myoclonic seizures are more likely overlooked than GTCS, the latter were analysed separately in a second step.

Statistics were performed with SPSS Statistics 23.0. Interval type data are given as median and interquartile range (IQR). Binary regression analysis (inclusion method: stepwise backward; $p < 0.05$ [p in], $p > 0.1$ [p out]; iteration 20; constant included) was performed to calculate odds ratios (OR) with 95% confidence intervals (CI) as estimates for variables independently associated with discontinuation of AEDs, overall seizure relapse, and GTCS relapse. Sex, family history of epilepsy, epilepsy syndrome, occurrence of GTCS, and age at seizure onset were included as independent variables. For seizure relapse, age at AED withdrawal and duration of seizure remission beforehand were additionally included; for GTCS relapse, duration of GTCS remission was included as well. Time courses after AED discontinuation were compared with Kaplan–Meier analysis and Tarone–Ware test. As the analyses were exploratory, multiple comparisons were not corrected for.

Results

Among the 343 outpatients with IGE, 65 were excluded due to follow-up of < 20 years and another 22 because of relevant data missing. Among the remaining 256 patients, 84 (33%) had discontinued their AEDs at least once, with or without the treating physician's consent [7]. AED discontinuation was independently associated with either EGTCS (syndrome) or absence of GTCS (seizure type), and with female sex (Table 1). AEDs were discontinued at a median age of 33 years (IQR 23–46) after a median seizure-free period of 7 years (IQR 3–11) and a median GTCS-free period of 8 years (IQR 5–12; $n = 69$).

Table 1 Demographic and epilepsy-related variables associated with AED withdrawal

	AED discontinued, $n = 84$	AED never discontinued, $n = 172$	OR (95% CI), multivariable[a]
Female sex, *n* (column %)	49 (58%)	81 (47%)	**1.8 (1.0–3.3); $p = 0.039$**
Age at seizure onset, median (IQR), years	13 (9–16)	13 (8–16)	0.96 (0.91–1.01); $p = 0.077$
IGE syndrome			
CAE, *n* (column %)	28 (33%)	54 (31%)	1
JAE, *n* (column %)	15 (18%)	37 (22%)	1.7 (0.68–4.2); $p = 0.26$
JME, *n* (column %)	14 (17%)	52 (30%)	1.1 (0.46–2.7); $p = 0.82$
EGTCS, *n* (column %)	27 (32%)	29 (17%)	**5.8 (2.0–16.6); $p \leq 0.001$**
Occurrence of GTCS, n (column %)	74 (88%)	170 (99%)	**0.07 (0.01–0.35); $p \leq 0.001$**
Family history of epilepsy, *n* (column %)	11 (13%)	19 (11%)	b
Age at AED withdrawal, median (IQR), years	33 (23–46)[c]	n/a	n/a
Seizure remission before AED withdrawal, median (IQR), years	7 (3–11)[d]	n/a	n/a
GTCS remission before AED withdrawal, median (IQR), years	8 (5–12)[e]	n/a	n/a
Duration of follow-up, median (IQR), years	44 (31–54)	43 (31–55)	Not included
Age at end of follow-up, median (IQR), years	57 (46–66)	58 (47–69)	Not included

n/a not applicable

[a]Stepwise backward binary regression; $n = 256$ cases included; Nagelkerke's $R^2 = 0.17$

[b]Excluded during stepwise backward regression

[c]$n = 83$, otherwise no information

[d]$n = 80$, otherwise no information

[e]$n = 69$, otherwise no GTCS before AED discontinuation or no information

After AED withdrawal, seizures recurred in 39 patients (46%). Thirty-five patients experienced GTCS after AED discontinuation (47% of those 74 who ever had GTCS) including one who then had her first GTCS. Median latency from AED withdrawal to seizure relapse was 11 months (IQR 1–48) and median latency to GTCS relapse was 15 months (IQR 2–53). Median follow-up after AED discontinuation was 20 years (IQR 9–32). Following multivariable analysis, recurrence of both any seizure type and of GTCS were independently associated with short duration of seizure freedom beforehand (Table 2; Fig. 1).

Patient numbers were too small to include seizure type combinations into the multivariable analysis. However, descriptively, those two JME patients with all three seizure types (myoclonic and absence seizures and GTCS) both relapsed after AED withdrawal (100%), compared to 1 out of 11 JME patients with myoclonic seizures and GTCS "only" (8%; none had myoclonic seizures only). Similarly, among patients with childhood and juvenile absence epilepsy, those

Table 2 Variables associated with seizure and GTCS relapse after AED withdrawal

	Seizure relapse, $n=39$	No seizure relapse, $n=45$	OR (95% CI), multivariable[a]	GTCS relapse, $n=35$	No GTCS relapse, $n=39$	OR (95% CI), multivariable[g]
Female sex, *n* (column %)	24 (62%)	25 (56%)	b	20 (57%)	23 (59%)	b
Age at seizure onset, median (IQR), years	14 (9–16)	12 (9–16)	b	14 (10–17)	13 (9–17)	b
IGE syndrome			b			
CAE, *n* (column %)	10 (26%)	18 (40%)		7 (20%)	12 (31%)	1
JAE, *n* (column %)	10 (26%)	5 (11%)		9 (26%)	5 (13%)	2.9 (0.63–13.4); $p=0.17$
JME, *n* (column %)	3 (8%)	11 (24%)		3 (9%)	11 (28%)	0.74 (0.14–4.0); $p=0.73$
EGTCS, *n* (column %)	16 (41%)	11 (24%)		16 (46%)	11 (28%)	3.5 (0.91–13.5); $p=0.067$
Occurrence of GTCS, *n* (column %)	37 (95%)	37 (82%)	5.0 (0.91–27.7); $p=0.064$	35 (100%)	23 (100%)	Not included
Family history of epilepsy, *n* (column %)	4 (10%)	7 (16%)	b	3 (9%)	6 (15%)	b
Age at AED withdrawal, median (IQR), years	32 (25–47)	36 (21–46)[c]	b	32 (23–47)	39 (29–47)[h]	b
Seizure remission before AED withdrawal, median (IQR), years	5 (1–8)[d]	8 (5–12)[c]	**0.87 (0.78–0.96); $p=0.008$**	5 (2–9)[i]	8 (5–12)[h]	**0.88 (0.78–0.99); $p=0.039$**
GTCS remission before AED withdrawal, median (IQR), years	7 (3–12)[e]	10 (5–14)[f]	(not included)	6 (3–12)[j]	10 (6–14)[h]	b

[a]Stepwise backward binary regression; $n=80$ cases included; Nagelkerke's $R^2=0.19$

[b]Excluded during stepwise backward regression

[c]$n=44$, otherwise no information

[d]$n=36$, otherwise no information

[e]$n=33$, otherwise no GTCS or no information

[f]$n=36$, otherwise no GTCS or no information

[g]Stepwise backward binary regression; $n=69$ cases included; Nagelkerke's $R^2=0.22$.

[h]$n=38$, otherwise no information

[i]$n=32$, otherwise no information

[j]$n=31$, otherwise no GTCS before AED discontinuation or no information

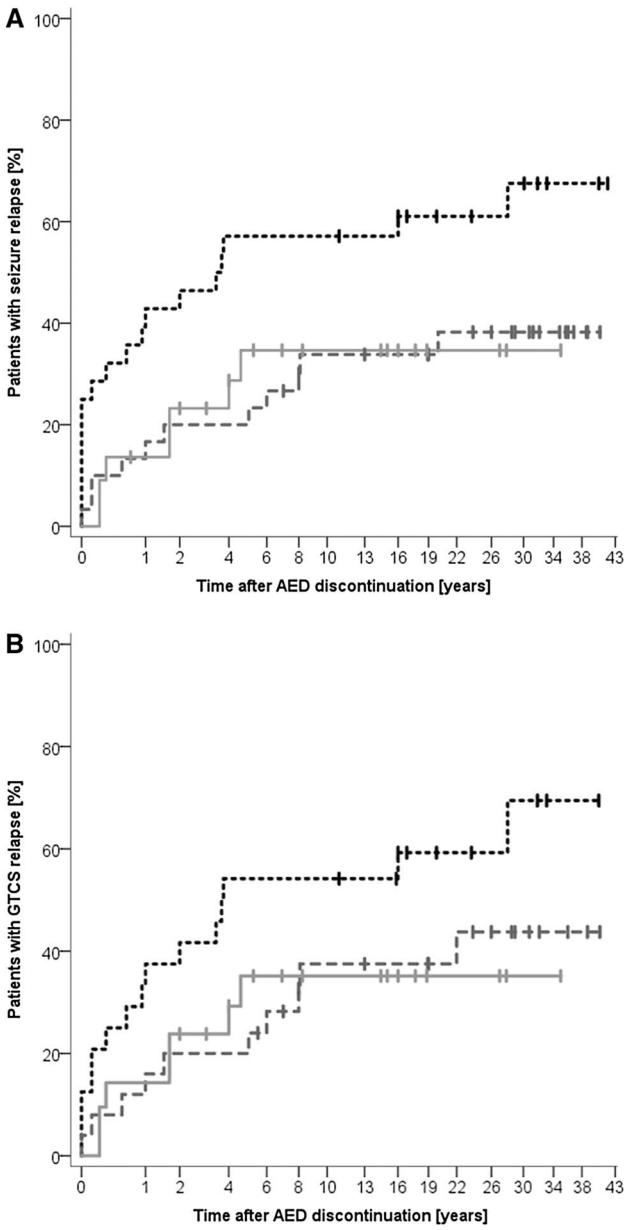

Fig. 1 Seizure and GTCS relapse rates after AED withdrawal**.** Overall seizure (**a**) and GTCS relapse rates (**b**) over time stratified by duration of seizure remission before AED withdrawal. For enhanced clearness, *X* axis scales were exponent-transformed. **a** 80 cases included; 4 not included due to missing information on duration of seizure remission. Seizure remission before AED withdrawal: 0 to < 5 years, black dotted line, $n = 28$; 5 to < 10 years, dark grey dashed line, $n = 30$; 10–35 years, light grey solid line, $n = 22$. Censored, vertical lines. Tarone–Ware test (uncorrected): 0 to < 5 years vs. 5 to < 10 years, $p = 0.015$; 0 to < 5 years vs. 10–35 years, $p = 0.039$; 5 to < 10 years vs. 10–35 years, $p = 0.89$. **b** 70 cases included; 10 not included due to lack of GTCS, 4 not included due to missing information on duration of seizure remission. Seizure remission before AED withdrawal: 0 to < 5 years, black dotted line, $n = 24$; 5 to < 10 years, dark grey dashed line, $n = 25$; 10–35 years, light grey solid line, $n = 21$. Censored, vertical lines. Tarone–Ware test (uncorrected): 0 to < 5 years vs. 5 to < 10 years, $p = 0.066$; 0 to < 5 years vs. 10–35 years, $p = 0.095$; 5 to < 10 years vs. 10–35 years, $p = 0.95$

33 with additional GTCS had a higher rate of seizure relapse (55%) than those 10 with absence seizures only (20%). Psychiatric comorbidity was not associated with seizure relapse (data not shown).

Discussion

Following AED withdrawal, more than half of adult IGE patients remained seizure-free. Seizure recurrence was associated with a short duration of seizure remission beforehand: if patients had been seizure-free for < 5 years, two-thirds relapsed, whereas among those in remission for ≥ 5 years, only one-third relapsed (Fig. 1). Regarding GTCS only, relapse risk and association with duration of prior seizure remission were similar.

The 46% overall seizure recurrence rate found here is lower than what has been reported in the literature. In one previous study, 80% of 164 IGE patients discontinuing their AEDs had a seizure relapse [15] while in another study, 52% of 44 relapsed [16]. These differences are presumably due to disparate patient characteristics: the latter study was performed in mostly adolescent IGE patients who withdrew after ≥ 2 seizure-free years [16] while the work presented here focused on adults. For the formerly mentioned study, age and duration of seizure freedom at AED withdrawal were not denoted [15].

Recent articles indicate that both higher age and longer time of seizure remission at AED discontinuation might lower the risk of subsequent seizure relapse. A meta-analysis on refractory JME reported 78% of 246 JME patients (95% CI 52–94%) to have recurrent seizures after AED discontinuation, with higher relapse rates in comparably younger patient cohorts [9]. Another meta-analysis on AED withdrawal in adolescents with all types of epilepsy identified, among others, short duration of seizure remission prior to AED discontinuation to be independently associated with seizure relapse [17]. Average data from the IGE patient cohort presented here were entered into the prediction nomogram derived from that meta-analysis. Depending on the respective number of seizures before remission, predicted 5-year seizure recurrence rates would be 60–72% compared to 39% in this real cohort. This also argues for adult patients as in the present study (median age at AED discontinuation: 33 years) having a better chance of sustained seizure-freedom than youths as in the meta-analysis (15 years).

Regarding the different IGE syndromes, previous studies found seizure recurrence rates to be relatively high in JME and low in CAE [15, 16]. In the study presented here, relapse rates were low both in JME (21%) and CAE (34%) compared to EGTCS (59%) and JAE (67%). This is very likely confounded by a more or less conservative selection of patients to discontinue their AEDs, ranging from 21% in

JME to 48% in EGTCS. Following multivariable analysis, specific IGE syndromes were not independently associated with seizure recurrence, mirroring homogeneous overall long-term seizure outcome within this patient cohort as previously reported [6, 13]. However, co-occurrence of GTCS in absence epilepsy and of absence seizures in JME both seemed related to increased rates of seizure relapse. Both constellations have already been shown to be associated with rather unfavourable overall seizure outcome [10, 14].

As the data presented here are retrospectively collected and partly based on patients' self-reports, some interesting aspects such as history of febrile seizures, number of seizures before remission, number of AEDs used, or EEG findings before withdrawal, were available for a minority of patients only and could, therefore, not be taken into account. Patients studied here were treated for many years in a single tertiary care centre, indicating a very likely selection bias towards difficult-to-treat epilepsy. Nevertheless, individuals with a rather benign course of IGE were presumably more likely counselled to discontinue their AEDs than those with a rather unfavourable course. This limitation can only be overcome by a prospective randomised study protocol.

Following the results outlined above, AED withdrawal in adult patients with long-standing IGE seems to bear a 50/50 chance of success. If seizure type constellations are not taken into account, IGE syndromes alone play a minor role for seizure recurrence. On the other hand, duration of seizure remission before AED withdrawal appears as a highly relevant risk factor. As a consequence, future patients with long-standing IGE should be seizure-free for at least 5 years before attempting to discontinue their AEDs.

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Compliance with ethical standards

Conflicts of interest Martin Holtkamp received speaker's honoraria and/or consultancy fees from Bial, Desitin, Eisai, LivaNova, Novartis, and UCB. All the other authors declare that they have no conflicts of interest.

Ethical standards The study was approved by the institutional review board at Charité–Universitätsmedizin Berlin and was, therefore, conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All interviewed patients or their next-of-kin gave written informed consent.

References

1. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshe SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM (2017) ILAE classification of the epilepsies: position paper of the ILAE Commission for Class Terminol. Epilepsia 58(4):512–521. https://doi.org/10.1111/epi.13709
2. Grosso S, Galimberti D, Vezzosi P, Farnetani M, Di Bartolo RM, Bazzotti S, Morgese G, Balestri P (2005) Childhood absence epilepsy: evolution and prognostic factors. Epilepsia 46(11):1796–1801. https://doi.org/10.1111/j.1528-1167.2005.00277.x
3. Berg AT, Levy SR, Testa FM, Blumenfeld H (2014) Long-term seizure remission in childhood absence epilepsy: might initial treatment matter? Epilepsia 55(4):551–557. https://doi.org/10.1111/epi.12551
4. Callenbach PM, Bouma PA, Geerts AT, Arts WF, Stroink H, Peeters EA, van Donselaar CA, Peters AC, Brouwer OF (2009) Long-term outcome of childhood absence epilepsy: Dutch Study of Epilepsy in Childhood. Epilepsy Res 83(2–3):249–256. https://doi.org/10.1016/j.eplepsyres.2008.11.011
5. Beghi M, Beghi E, Cornaggia CM, Gobbi G (2006) Idiopathic generalized epilepsies of adolescence. Epilepsia 47(Suppl 2):107–110. https://doi.org/10.1111/j.1528-1167.2006.00706.x
6. Vorderwulbecke BJ, Kowski AB, Kirschbaum A, Merkle H, Senf P, Janz D, Holtkamp M (2017) Long-term outcome in adolescent-onset generalized genetic epilepsies. Epilepsia 58(7):1244–1250. https://doi.org/10.1111/epi.13761
7. Syvertsen M, Flogstad I, Enger U, Landmark CJ, Koht J (2019) Antiepileptic drug withdrawal in juvenile myoclonic epilepsy. Acta Neurol Scand 139(2):192–198. https://doi.org/10.1111/ane.13042
8. Hofler J, Unterberger I, Dobesberger J, Kuchukhidze G, Walser G, Trinka E (2014) Seizure outcome in 175 patients with juvenile myoclonic epilepsy—a long-term observational study. Epilepsy Res 108(10):1817–1824. https://doi.org/10.1016/j.eplepsyres.2014.09.008
9. Stevelink R, Koeleman BP, Sander JW, Jansen FE, Braun KP (2018) Refractory juvenile myoclonic epilepsy: a meta-analysis of prevalence and risk factors. Eur J Neurol. https://doi.org/10.1111/ene.13811
10. Senf P, Schmitz B, Holtkamp M, Janz D (2013) Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. Neurology 81(24):2128–2133. https://doi.org/10.1212/01.wnl.0000437303.36064.f8
11. Holtkamp M, Senf P, Kirschbaum A, Janz D (2014) Psychosocial long-term outcome in juvenile myoclonic epilepsy. Epilepsia 55(11):1732–1738. https://doi.org/10.1111/epi.12751
12. Holtkamp M, Kowski AB, Merkle H, Janz D (2014) Long-term outcome in epilepsy with grand mal on awakening: forty years of follow-up. Ann Neurol 75(2):298–302. https://doi.org/10.1002/ana.24103
13. Holtkamp M, Janz D, Kirschbaum A, Kowski AB, Vorderwulbecke BJ (2018) Absence epilepsy beyond adolescence: an outcome analysis after 45 years of follow-up. J Neurol Neurosurg Psychiatry 89(6):603–610. https://doi.org/10.1136/jnnp-2017-317052
14. Trinka E, Baumgartner S, Unterberger I, Unterrainer J, Luef G, Haberlandt E, Bauer G (2004) Long-term prognosis for childhood and juvenile absence epilepsy. J Neurol 251(10):1235–1241. https://doi.org/10.1007/s00415-004-0521-1
15. Nicolson A, Appleton RE, Chadwick DW, Smith DF (2004) The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies. J Neurol Neurosurg Psychiatry 75(1):75–79

16. Pavlovic M, Jovic N, Pekmezovic T (2011) Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. Seizure 20(7):520–525. https://doi.org/10.1016/j.seizure.2011.03.007
17. Lamberink HJ, Otte WM, Geerts AT, Pavlovic M, Ramos-Lizana J, Marson AG, Overweg J, Sauma L, Specchio LM, Tennison M, Cardoso TMO, Shinnar S, Schmidt D, Geleijns K, Braun KPJ (2017) Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. Lancet Neurol 16(7):523–531. https://doi.org/10.1016/S1474-4422(17)30114-X