Epilepsy Research (2014) 108, 1221—1227

journal homepage: www.elsevier.com/locate/epilepsyres

# Natural course and predictors of spontaneous seizure remission in idiopathic generalized epilepsy: 7—27 years of follow-up

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Received 7 October 2013; received in revised form 5 March 2014; accepted 27 April 2014
Available online 14 May 2014

**KEYWORDS**
Idiopathic generalized epilepsy;
Spontaneous course;
Long-term seizure outcome

**Summary** The spontaneous course of idiopathic generalized epilepsy (IGE) is still controversial. The aim of this study was both to investigate the long-term spontaneous course and to identify factors that are predictive for epilepsy remission in a small cohort of 15 IGE patients (9 women) who refused antiepileptic drug (AED) treatment and therefore never have been treated with AED.

All of them were reevaluated with a review of their medical records and direct face-to-face interview; the mean duration of follow-up was 15.3 years. Five (33.3%) of them had absence epilepsy (absence seizures, ABS), 5 had IGE with generalized tonic—clonic seizures (GTCS), and another 5 had both seizure types (IGE with ABS/GTCS). Rate of epilepsy remission was 53.3% with a mean time of seizure freedom of 13.1 years; rate of remission was highest among absence epilepsy patients (80%), followed by IGE with GTCS (60%) and IGE with ABS/GTCS (20%). The frequency of spontaneous generalized interictal epileptiform discharges in electroencephalography is not associated with the long-term seizure outcome ($p = 0.201$) and per se does not require AED treatment. Furthermore, the occurrence of photoparoxysmal responses ($p = 0.020$)

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http://dx.doi.org/10.1016/j.eplepsyres.2014.04.004

as well as the occurrence of more than 3 GTCS during the course ($p = 0.029$) were identified as significant predictors for a poor long-term seizure outcome which makes AED treatment indispensable in these patients. This study underlines the heterogenity of the group of IGE. AED treatment has no impact on the spontaneous course of IGE with ABS and/or GTCS. Several predictors for the long-term seizure outcome in patients with IGE were identified in this study.


## Introduction

Idiopathic generalized epilepsies (IGE) are genetically determined epilepsy syndromes (Weber et al., 2011) with a prevalence of 15—30% among all patients with epilepsy (Jallon and Latour, 2005; Mohanraj and Brodie, 2007) and characterized by different combinations of primary generalized seizure types — such as absence seizures (ABS), generalized tonic—clonic seizures (GTCS), and bilateral myoclonic seizures (BMS) (Niedermeyer, 1996; Duncan, 1997; Benbadis, 2005) — age-dependent seizure onset, typical pathological EEG patterns (Weber et al., 2011), and the lack of apparent MRI abnormalities (Mattson, 2003). The interictal electroencephalography (EEG) shows generalized interictal epileptiform discharges (GIED) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and the neurological examination and overall intelligence are normal (Adie, 1924; Niedermeyer, 1996). Childhood and juvenile absence epilepsy (CAE, JAE), juvenile myoclonic epilepsy (JME), and IGE with generalized tonic—clonic seizures (GTCS) on awakening are the best defined IGE syndromes (Berg et al., 2010; Weber et al., 2011).

The majority of earlier studies analyzes the prognosis of IGE as a group, only a few focus on different IGE syndromes. IGE as a group is considered to be highly responsive to antiepileptic drug (AED) treatment. Assuming appropriate AED treatment, general remission rate of IGE is reported to be 60—90% (Annegers et al., 1979; Berg et al., 2001; Sillanpää and Schmidt, 2006; Mohanraj and Brodie, 2007; Kharazmi et al., 2010; Szaflarski et al., 2010). With regard to individual IGE syndromes, remission rate is reported to be 65—90% in absence epilepsies, 65—85% in IGE with GTCS, 50—80% in IGE with ABS and GTCS, and 64.4—88% in JME (Groh, 1975; Annegers et al., 1979; Janz et al., 1983; Dieterich et al., 1985; Panayiotopoulos et al., 1994; Berg et al., 2001; Baykan et al., 2008; Camfield and Camfield, 2009; Geerts et al., 2010; Baykan et al., 2013). Janz (1969) reported seizure remission in 16% of his CAE patients and in 10—30% of his patients with IGE with GTCS. In another study, Wirrell et al. (1996) found 65% of their patients with absence epilepsy being seizure-free after a follow-up of 14 years. Cognitive impairment at epilepsy onset, epileptic absence status, ongoing GTCS or myoclonic seizures despite AED treatment, GTCS in first-degree relatives, and pathological EEG background activity were identified as predictors for a poor long-term seizure outcome (Wirrell et al., 1996). In a study on 119 patients with CAE, Grosso et al. (2005) reported the seizure outcome to be greatly influenced by the diagnostic criteria used to select patients, suggesting that stricter diagnostic criteria allow to define a more homogeneous group of patients, which may help to better forecast the seizure outcome. Factors predicting unfavorable prognosis were GTCS, myoclonic seizures, and EEG discharges atypical for CAE.

Only few studies investigated the seizure outcome after AED withdrawal and report seizure remission in 30—50% among all epilepsies irrespective the type and etiology (Zielinski, 1974; Keränen and Riekkinen, 1993). Although clear evidence is lacking, long-term seizure-freedom after AED withdrawal can result from a change of epileptogenicity. Several authors found that AED withdrawal did not change the rates of long-term seizure outcome of idiopathic epilepsies (Kwan and Sander, 2004; Geerts et al., 2010), however, the effects of AED treatment on the spontaneous course of IGE still remain unclear. Geerts et al. (2010) revealed an association with the spontaneous course only for the type and etiology of the epilepsy. Although current medical therapies for epilepsy are symptomatic therapies, as they suppress seizure activity but do not cure the underlying mechanisms, several recent experimental studies reported success of medical interference with epileptogenesis (Blumenfeld et al., 2008; Dezsi et al., 2013; Wong, 2010). However, there are no studies on the spontaneous course of IGE in patients who have never been treated with AED.

The aim of this study was to investigate the spontaneous course of IGE in a cohort of patients who refused AED treatment from the beginning of their epilepsy and, therefore, never have been treated with AED. Furthermore we aimed to identify factors that are predictive for seizure remission in these patients.

## Materials and methods

This retrospective study was approved by the University of Greifswald Institutional Review Board. The study was conducted among the inhabitants of the catchment area of the University Hospital of Greifswald (total population ~500,000) in the northeast of Germany. Inclusion criteria were (1) diagnosis of IGE, (2) no prior treatment with AED, and (3) normal neurological examination and overall intelligence. Data from all patients diagnosed with IGE before January 2000 were retrospectively reviewed from the Epilepsy Center database. Diagnosis of IGE was made by experienced epileptologists on the basis of the patients' medical history and medical history by witnesses as well as the patients' EEG; diagnostic criteria of IGE included the history of BMS, GTCS, and ABS, alone or in combination. EEG studies at the time of diagnosis were performed in all patients using the international 10—20 system of electrode placement. Not to treat IGE patients with AED was not common practice in our epilepsy center and only attempted if desired by the patient, all patients selected for the study