Debate: Can we predict with reasonable confidence which patients with idiopathic generalized epilepsy will remit?

Position: No

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The subgroup of generalized epilepsies which for decades has been known as ‘idiopathic’ has now been suggested to be termed ‘genetic’. Beyond terminology, the conceptual considerations however are very similar, and idiopathic / genetic epilepsy is, ‘as best as understood, the direct result of a known or presumed genetic defect in which seizures are the core symptom of the disorder’ (Berg et al. 2010). Prevalence studies consistently demonstrate that idiopathic generalized epilepsies (IGE) make up 15 to 20 % of all epilepsies. IGE subsyndromes are characterized and defined by age at onset of epilepsy and by the predominant seizure type. Three IGE subsyndromes commonly commence in adolescence, i.e. between the age of 12 and 18 years. These comprise juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with grand mal only either manifesting on awakening (EGMA) or by random (EGMR). Long-term seizure outcome in regard of remittance even after withdrawal of antiepileptic drugs may be non-congruent in these subsyndromes. In IGE, long-term seizure outcome data are not available from prospectively followed incidence cohorts, but only from retrospective prevalence cohorts.

In an Austrian study, 64 JAE patients had a follow-up of 22 years, 37 % were seizure free in the terminal 2 years, the vast majority was still treated antiictally (Trinka 2004). A meta-analysis on childhood absence epilepsy and JAE with 27 % of patients being adolescents or adults at absence epilepsy onset revealed terminal seizure freedom

(duration depended on time of follow-up which was heterogeneous) in 59 % of patients (Bouma et al. 1996). Absence epilepsies without generalized tonic clonic seizures had a more favorable outcome (78 % seizure-free) than those with generalized tonic clonic seizures (35 %). Another predictor for long-term seizure freedom in absence epilepsies was older age; the older the patients were and thus the longer epilepsy has lasted, the less likely they still had seizures.

Until some years ago, the axiomatic dogma was that JME requires lifelong antiictal treatment, otherwise seizure recurrence would be almost inevitable. In the last couple of years, five retrospective studies on long-outcome of JME have been published. A total of 208 patients were followed up for at least 20 years (for summary, see Syvertsen et al. 2014). Five-year seizure remission was seen between 27 and 68 %, and for at least 5 years, 8 to 26 % of all patients in addition to seizure freedom were off antiictal medication. Out of 45 patients who were off medication at the end of the study, 31 were seizure free for at least 5 years. However, it is unclear how many patients in the course of their disease had seizure relapse after withdrawal of antiictal medication and then restarted regular drug intake.

Our center identified manifestation of additional absence seizures at onset of JME as an independent predictor for lack of terminal 5-year seizure remission (Senf et al. 2014). In univariate analysis, other studies demonstrated that long duration of epilepsy with unsuccessful treatment, antiictal polytherapy, and generalized tonic clonic seizures preceded by bilateral myoclonic seizures are significantly associated with lack of seizure freedom. There was a general trend that the older the patients were, the more likely they were in remission.

In the early course of EGMA, favorable treatment response to antiictal substances is well known, but until recently long-term data on seizure prognosis had not been available. We reported 42 patients with a ‘pure’ form of EGMA lacking absence

seizures and myoclonia (Holtkamp et al. 2014). Patients had a mean follow-up of 40 years, and 26 subjects (62 %) had been seizure-free for at least the last 5 years. Only five seizure-free patients were off antiictal medication. We identified current age to be the only independent predictor for lacking seizure freedom in the terminal 5 years. Remission rates were 35.7% in patients 55 years and younger (n = 14), 66.7% in patients aged between 56 and 65 years (n = 12), and 81.3% in patients older than 65 years (n = 16).

Withdrawal of antiictal substances had been performed in 19 patients (45.2%), 12 of which had seizure relapse (63.2%). Mean time between withdrawal and relapse was 22 $\pm$ 31 months (median 7 months). We do not know how many of the 23 continuously treated patients would still be seizure free, if antiictal drugs had been withdrawn in the course of the disease. This, however, was done rather reluctantly due to our early experiences regarding seizure relapse after withdrawal of antiictal agents.

In a Canadian population-based study, 40 patients with epilepsy with grand mal by random were reported (Camfield & Camfield 2010). In 33 patients, antiictal drugs had been withdrawn and 27 of those patients (75 %) were seizure-free for more than 15 years. These findings are in line with 15 of our patients with EGMR, 12 of those (80 %) were seizure-free in the last 5 years (Holtkamp et al. 2014 Ann Neurol).

To conclude, currently available data are based on single-center retrospective studies revealing heterogeneous findings in regard of seizure remittance. Roughly speaking, probability of seizure freedom within the last 5 years is determined by higher age, but the majority of patients are still on antiepileptic drugs. Up to now, published data do not allow to sufficiently predict which IGE patients will remain seizure-free after antiepileptic drug withdrawal.

References

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