

Idiopathic (primary) generalized epilepsy

Traditional versus new antiepileptic drugs

Samira Yadegari, MD, Parviz Bahrami, MD.

ABSTRACT

أظهرت الدراسات العصبية والأشعة أن الصرع العام المجهول السبب ينشأ من تشنجات. تظهر أعراض مختلفة بالإعتماد على بدء الأعراض، ونوع التشنجات الظاهرة. يهدف هذا التقرير لإيجاز خصائصه، والتوقعات، وخيارات الأدوية المضادة للصرع. بالإضافة إلى ذلك قمنا بمراجعة الدور المتطور للأدوية المضادة للصرع في أعراض محددة للصرع العام المجهول السبب. أن أكثر التجارب الدوائية أظهرت أن أثر الأدوية الجديدة المضادة للصرع والتي قد قامت بمقارنة أثره على الأدوية الوهمية وليس بالأدوية المضادة للاختلاج. أن الأطار الواسع للأدوية المضادة للصرع الحديثة تعد من الخيارات الأولى في أعراض معينة، يعد العلاج والأثر العصبي المهم الخيار التالي للوقاية من هذا الصرع لدى المرضى المقاومين للعلاج. كما يجب على أخصائي الأعصاب الأخذ بعين الاعتبار نوع السمات الدائمة، وجنس المريض، والإعتلال المشترك، والأدوية المضادة للصرع التي تزيد من نوع محدد للتشنجات.

Idiopathic generalized epilepsies (IGE) are genetic based seizures with normal neurologic exam, intelligence, and imaging studies. Based on the age of onset and prominent seizure type, different syndromes were identified. The purpose of this study is to summarize the characteristics, prognosis, and choices of antiepileptic drugs (AED) in common syndromes of IGE. In addition, we review the updated role of new AEDs in specific syndromes of IGE. The first choice AED is usually valproate. Most drug trials on the effects of new AEDs compared them with placebo and not valproate. However, some of the broad spectrum new AEDs may be considered as the first choice in specific conditions. In true refractory patients, combination therapy and vagal nerve stimulation could be the next option. In the proper management of IGE, neurologists should consider the predominant seizure type, patient gender, co-morbidities, and antiepileptic drugs that may aggravate a specific seizure type.

Neurosciences 2013; Vol. 18 (2): 117-121

From the Department of Neurology (Yadegari), Tehran University of Medical Sciences, Tehran, and the Department of Epilepsy (Bahrami), Lorestan University of Medical Sciences, Lorestan, Iran.

Address correspondence and reprint request to: Dr. Samira Yadegari, Shariati Hospital, North Karegar Street, Tehran 14114, Iran. Tel. +98 2184902224. Fax. +98 88220029. E-mail: yadegarisamira@yahoo.com

Idiopathic generalized epilepsies (IGE) account for 20% of all epilepsies,¹ and refer to a diverse group of epileptic seizures and syndromes, which usually have a genetic basis.²⁻⁴ In the new classification of the International League Against Epilepsy (ILAE) in 2010,² the terminology was changed. In this new classification, the causes were categorized as genetic, metabolic and structural, and unknown groups versus the old terminology of idiopathic, symptomatic, and cryptogenic. Idiopathic also refers to primary generalized epilepsy in prior classifications (before 1989), versus secondary (and cryptogenic) generalized epilepsy.⁵ Idiopathic generalized epilepsies usually have no identifiable underlying structural or anatomic causes, and neuroimaging is normal. Seizure types in IGE include myoclonic, absence, and generalized tonic-clonic (GTC) seizures. Patients with IGE usually have normal intelligence, and a normal neurologic exam.⁶⁻⁸ In their electroencephalogram (EEG), there is no background abnormality such as slowing. In the new ILAE report, IGE share the phenotype of either 3 Hz spike-and-wave or rapid (>3Hz) spike-and-wave.⁹ Indeed, these seizures are a spectrum of a single condition with different

Disclosure. The authors declare no conflicting interests, support or funding from any drug company.

phenotypes. Although they are categorized as general epilepsies, which originate and distribute bilaterally, asymmetrical presentation also can occur.³ Therefore, asymmetry alone is not opposed to the diagnosis of IGE. This study aims to summarize the characteristics, prognosis, and choices of antiepileptic drugs (AEDs) in common syndromes of IGE. In addition, we review the updated role of new AEDs in specific syndromes of IGE. For this purpose, we searched PubMed, Ovid, and Scopus databases from 2001 to 2012 with key words consisting of IGE, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, antiepileptic drug, and refractory IGE. Studies relevant to our aims were included.

Specific syndromes of IGE. Distinct syndromes of IGE were identified based on age of onset and prominent seizure type including benign neonatal and infantile idiopathic generalized epilepsies, childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and GTC only. However, some of the idiopathic syndromes such as benign myoclonic epilepsy of infancy were included in the unknown category in the new classification.² In IGE, a syndrome may evolve to another. In addition, different members of a family may have different IGE syndromes.³

Childhood absence epilepsy (*petit mal*).^{3,10-12} The most widely recognized absence seizure. Age: 4 to 8 years. Gender: female more than male. Features: sudden onset with loss of consciousness and sudden termination with continuing of the previous activity, short duration (several seconds), commonly associated with automatisms including eye blinking. EEG: the typical 3 Hz (2.5–3.5 Hz) spike-wave complexes may be aggravated by hyperventilation. Prognosis: good especially in males (most patients become seizure free), presence of other seizure types such as GTC and polyspike in EEG are negative prognostic factors.

Juvenile absence epilepsy.¹²⁻¹⁴ Age: 10 to 17 years. Gender: female more than male. Features: between CAE and JME. Consciousness less impaired than CAE. Generalized and myoclonic seizures are more common than CAE. EEG: generalized spike-and-wave discharges, faster but less regular and rhythmic than CAE. Induced by hyperventilation. Photosensitivity is unusual. Prognosis: uncertain (long term evolution has not yet been fully determined).

Juvenile myoclonic epilepsy.^{3,11,15} Age: 8 to 20 years (mean: 14.6). Gender: equal in female and male. Features: presents with (1) GTC seizure, (2) the main symptom is a myoclonic jerk with variable amplitude, often occurs 30 minutes after awakening in the

morning, (3) absence seizure occurs in 30%. EEG: high-amplitude generalized, symmetric and synchronous 4–6 Hz polyspike-wave complexes, highest rate of photosensitivity of all epilepsies. Prognosis: uncertain (long life treatment is usually required).

Idiopathic generalized epilepsy with generalized tonic-clonic seizures.^{11,16} Probably the most common type of IGE in adult neurology practice. Age: 6 to 24 years (more in young adulthood). Gender: equal in male and female. Features: GTC seizures mostly after awakening, may be photosensitive. EEG: mixture of generalized epileptiform discharges of any type, shifting asymmetry. Prognosis: good.

Treatment of IGE. Up to 84% of IGE patients achieve complete seizure control.^{1,17} One of the most common causes of treatment failure is “pseudo intractability,”³ which could be due to misdiagnosis of IGE, incorrect typing of epileptic syndrome, choosing an inappropriate AED, and poor compliance.^{11,18} For example, staring episodes of absence seizure may be misdiagnosed as a complex partial seizure, and subsequently, GTC seizures misinterpreted as rapidly secondary GTC seizures. Failure to detect a myoclonic seizure in JME and prescribing carbamazepine can lead to aggravation of myoclonic jerks. Other drugs, which can aggravate myoclonus include phenytoin (its effect is weaker than carbamazepine), lamotrigine, gabapentin, and vigabatrin. Furthermore, carbamazepine, phenytoin, gabapentin, and tiagabine are AEDs that may aggravate absence seizure.^{10,19,20} Hence, the first step in treatment of IGE is the correct diagnosis. If distinction of IGE is not clear after history, physical exam, and interictal EEG, then video EEG monitoring and neuroimaging may be needed. After that, caution should be taken to avoid prescribing an inappropriate AED that may aggravate a specific type of seizure in IGE.^{20,21} In several reviews on the first choice AED in IGE, sodium valproate is still recommended.^{1,10,17} New drugs with a broad spectrum of action such as lamotrigine, levetiracetam, and topiramate are increasingly used in the treatment of IGE, but evidence for treatment of IGE with new AEDs is not as available as in partial epilepsies. Only a few controlled clinical trials have been conducted to compare the effectiveness of new AEDs versus valproate in IGE,^{22,23} and most of drug trials have assessed seizure control compared with placebo.^{4,24}

Absence epilepsy (CAE, JAE). Class 1 evidence supports that valproate and ethosuximide are equally effective in the treatment of absence seizures.²³ In patients with other types of seizure, such as GTC seizures, which may develop in 40% of CAE,¹⁸ valproate is the first choice because it has a broad spectrum of

action. Ethosuximide is recommended in patients younger than 10 years.¹⁰ Lamotrigine is the second line option in absence epilepsy,^{22,25} however, a comparative randomized study in 38 children aged from 3-13 years with CAE or JAE showed that lamotrigine could be used as initial monotherapy in typical absence seizures,²⁶ although onset of action was faster with valproate. Patients who fail to respond to lamotrigine, valproate, and ethosuximide alone, may be controlled with a combination of these drugs. Sedation and tolerability limit the use of benzodiazepines. Adjunctive levetiracetam has effectively controlled seizures in IGE, including JAE with onset during adolescence in 2 randomized placebo-controlled trials.²⁴ There is insufficient evidence in favor of using zonisamide and topiramate in absence epilepsy.^{10,11,18}

Juvenile myoclonic epilepsy. The first step in the treatment of JME is modifying the lifestyle and elimination of precipitating factors of seizures including sleep deprivation, fatigue, and excessive intake of alcohol.¹¹ In the pharmacologic treatment of JME, the first choice is valproate, which controls 3 types of seizures in JME. In responders, a low dose of valproate (10-20 mg/kg) is adequate for seizure control.²⁷ In the following conditions, lamotrigine or topiramate should be considered as an alternative drug of choice: 1) adverse effects or intolerability of valproate, 2) resistance to valproate monotherapy, which occurs in 10-20% of JME patients,¹⁸ 3) in a woman with JME who is of childbearing age, new AEDs are the first choice because of their lower risk of teratogenicity, and 4) in obese patients with JME, zonisamide, or topiramate are useful. The later also will be a good option when migraine is accompanied with JME.^{28,29} In a randomized controlled trial comparing topiramate and valproate in JME, 8 of 12 (67%) in the topiramate group, and 4 of 7 (57%) in the valproate group were seizure-free in the period of treatment (12 weeks).³⁰ If myoclonic seizures continue on treatment with lamotrigine or topiramate, low doses of clonazepam can be effective,^{10,11} levetiracetam and zonisamide could be other options.^{24,31} Refractory cases may respond to phenobarbital/primidone,^{18,32} or a combination of valproate and lamotrigine when either monotherapy fails to treat myoclonic epilepsy.³³

Idiopathic generalized epilepsy with generalized tonic-clonic seizures. The drug of choice that effectively controls GTC seizures is valproate.^{3,11} Carbamazepine and phenytoin usually are used in partial epilepsies and ill-advised in IGE with GTC.³ Topiramate is the only new AED approved by the United States Food and Drug Administration in primary GTC seizures.^{34,35} Recently, lamotrigine was considered for the treatment of GTC

seizures in IGE. Three randomized placebo-controlled trials have suggested that adjunctive lamotrigine was effective in controlling primary GTC seizures.³⁶⁻³⁸ A once-daily extended release formulation of lamotrigine was used in one of these studies, which was more effective than placebo regarding the median percentage reduction of seizures from baseline.³⁸ Adjunctive levetiracetam has been well tolerated as long term treatment of IGE in patients aged from 4 to 65 years.³⁹

Refractory idiopathic generalized epilepsy. Refractory epilepsy has no uniform definition, but it is considered after failure to respond to 3 or more AEDs. Idiopathic generalized epilepsy, generally responds well to adequate treatment, and intractability is rare. It is unclear how many refractory patients with IGE have true refractory disease and are not pseudo-intractable. For severe refractory patients, vagal nerve stimulation (VNS) or felbamate could be considered.¹⁷ Although VNS was initially approved only for partial epilepsy, recent meta-analysis and interventional studies demonstrated that adjunctive VNS was also effective and safe in IGE.^{40,41} Nevertheless, complete seizure control with VNS is rare in refractory epilepsies.⁴¹ The ketogenic diet is a low carbohydrate and high fat diet, which can be recommended as an alternative to AED in pediatric patients with difficult to control absence seizures.⁴² A review of 17 published studies on absence epilepsy showed that 69% of 133 patients who received a ketogenic diet had more than 50% seizure reduction from baseline, and 34% of them became seizure free.⁴³ In a systematic review of MEDLINE, Current Contents, and the Cochrane library from 1987 to 2003 conducted by the American Academy of Neurology on new AEDs in the treatment of refractory epilepsies,⁴⁴ topiramate was recommended in the treatment of refractory primary GTC epilepsy in adults and children. The evidence for recommendation of other new AEDs like lamotrigine and levetiracetam was not sufficient.⁴⁴

In conclusion, IGE usually respond well to treatment; however, the occurrence of multiple seizures types in IGE sometimes makes the treatment challenging. Furthermore, intractability and pseudo-intractability are not uncommon. In general, valproate is still the first choice in IGE. In absence seizures, valproate has equal efficacy with ethosuximide. Broad spectrum new AEDs such as lamotrigine and topiramate could be the first choice as monotherapy or adjunctive therapy in specific conditions. They are cost effective when patients fail to respond to older drugs or intolerance due to adverse effects of older drugs. At this time, the data on the use of levetiracetam and zonisamide as monotherapy in IGE is insufficient. In placebo-controlled trials, adjunctive

levetiracetam has effectively controlled IGE syndromes. To choose the most proper antiepileptic drug in IGE, predominant seizure type, and co-morbid conditions of the patient should be considered.

References

- Curatolo P, Moavero R, Lo Castro A, Cerminara C. Pharmacotherapy of idiopathic generalized epilepsies. *Expert Opin Pharmacother* 2009; 10: 5-17.
- Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51: 676-685.
- Benbadis SR. Practical management issues for idiopathic generalized epilepsies. *Epilepsia* 2005; 46: 125-132.
- French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs, II: Treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2004; 45: 410-423.
- Panayiotopoulos CP. The new ILAE report on terminology and concepts for organization of epileptic seizures: a clinician's critical view and contribution. *Epilepsia* 2011; 52: 2155-2160.
- Gallentine WB, Mikati MA. Genetic generalized epilepsies. *J Clin Neurophysiol* 2012; 29: 408-419.
- Asadi-Pooya AA, Emami M, Sperling MR. A clinical study of syndromes of idiopathic (genetic) generalized epilepsy. *J Neurol Sci* 2013; 324: 113-117.
- Briellmann RS, Torn-Broers Y, Berkovic SF. Idiopathic generalized epilepsies: do sporadic and familial cases differ? *Epilepsia* 2001; 42: 1399-1402.
- Shinnar S. The new ILAE classification. *Epilepsia* 2010; 51: 715-717.
- Bourgeois BF. Chronic management of seizures in the syndromes of idiopathic generalized epilepsy. *Epilepsia* 2003; 44 (Suppl 2): 27-32.
- Sullivan JE, Dlugos DJ. Idiopathic Generalized Epilepsy. *Curr Treat Options Neurol* 2004; 6: 231-242.
- Loiseau P. Childhood absence epilepsy and related syndromes. In: Roger J, editor. *Epileptic Syndromes in Infancy, Childhood, and Adolescence*. Eastleigh (UK): John Libbey; 2002. p. 285-303.
- Seneviratne U, Cook M, D'Souza W. The prognosis of idiopathic generalized epilepsy. *Epilepsia* 2012; 53: 1079-2090.
- Aiguabella Macau M, Falip Centellas M, Veciana de Las Heras M, Climent Perin MA, Miró Lladó J, Moreno Gómez I, et al. Long term prognosis of juvenile absence epilepsy. *Neurologia* 2011; 26: 193-199.
- Renganathan R, Delanty N. Juvenile myoclonic epilepsy: under-appreciated and under-diagnosed. *Postgrad Med J* 2003; 79: 78-80.
- Unterberger I, Trinka E, Luef G, Bauer G. Idiopathic generalized epilepsies with pure grand mal: clinical data and genetics. *Epilepsy Res* 2001; 44: 19-25.
- Faught E. Treatment of refractory primary generalized epilepsy. *Rev Neurol Dis* 2004; 1 (Suppl 1): S34-S43.
- Perucca E. The management of refractory idiopathic epilepsies. *Epilepsia* 2001; 42 Suppl 3: 31-35.
- Carrazana EJ, Wheeler SD. Exacerbation of juvenile myoclonic epilepsy with lamotrigine. *Neurology* 2001; 56: 1424-1425.
- Benbadis SR, Tatum WO 4th, Gieron M. Idiopathic generalized epilepsy and choice of antiepileptic drugs. *Neurology* 2003; 61: 1793-1795.
- Murthy J. Seizure aggravation with antiepileptic drugs in idiopathic generalized epilepsies. *Neurol India* 2011; 59: 51-52.
- Mazurkiewicz-Beldzińska M, Szmuda M, Matheisel A. Long-term efficacy of valproate versus lamotrigine in treatment of idiopathic generalized epilepsies in children and adolescents. *Seizure* 2010; 19: 195-197.
- Beydoun A, D'Souza J. Treatment of idiopathic generalized epilepsy - a review of the evidence. *Expert Opin Pharmacother* 2012; 13: 1283-1298.
- Rosenfeld WE, Benbadis S, Edrich P, Tassinari CA, Hirsch E. Levetiracetam as add-on therapy for idiopathic generalized epilepsy syndromes with onset during adolescence: analysis of two randomized, double-blind, placebo-controlled studies. *Epilepsy Res* 2009; 85: 72-80.
- Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. *Epilepsia* 2004; 45: 1049-1053.
- Valencia I, Piñol-Ripoll G, Khurana DS, Hardison HH, Kothare SV, Melvin JJ, et al. Efficacy and safety of lamotrigine monotherapy in children and adolescents with epilepsy. *Eur J Paediatr Neurol* 2009; 13: 141-145.
- Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomized controlled trial. *Lancet* 2007; 369: 1016-1026.
- Montouris G, Abou-Khalil B. The first line of therapy in a girl with juvenile myoclonic epilepsy: should it be valproate or a new agent? *Epilepsia* 2009; 50 Suppl 8: 16-20.
- Isojarvi JI, Tauboll E, Herzog AG. Effect of antiepileptic drugs on reproductive endocrine function in individuals with epilepsy. *CNS Drugs* 2005; 19: 207-223.
- Levisohn PM, Holland KD. Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison. *Epilepsy Behav* 2007; 10: 547-552.
- Krauss GL, Betts T, Abou-Khalil B, Gergey G, Yarrow H, Miller A. Levetiracetam treatment of idiopathic generalised epilepsy. *Seizure* 2003; 12: 617-620.
- Kao A, Rao PM. Idiopathic generalized epilepsies. *Handb Clin Neurol* 2012; 107: 209-224.
- Mattson RH. Overview: idiopathic generalized epilepsies. *Epilepsia* 2003; 44 Suppl 2: 2-6.
- Bergey GK. Evidence-based treatment of idiopathic generalized epilepsies with new antiepileptic drugs. *Epilepsia* 2005; 46 Suppl 9: 161-168.
- Arroyo S, Dodson WE, Privitera MD, Glauser TA, Naritoku DK, Dlugos DJ, et al. Randomized dose-controlled study of topiramate as first-line therapy in epilepsy. *Acta Neurol Scand* 2005; 112: 214-222.
- Biton V, Sackellares JC, Vuong A, Hammer AE, Barrett PS, Messenheimer JA. Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. *Neurology* 2005; 65: 1737-1743.

37. Trevathan E, Kerls SP, Hammer AE, Vuong A, Messenheimer JA. Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. *Pediatrics* 2006; 118: e371-e378.
38. Biton V, Di Memmo J, Shukla R, Lee YY, Poverennova I, Demchenko V, et al. Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study. *Epilepsy Behav* 2010; 19: 352-358.
39. Delanty N, Jones J, Tonner F. Adjunctive levetiracetam in children, adolescents, and adults with primary generalized seizures: open-label, noncomparative, multicenter, long-term follow-up study. *Epilepsia* 2012; 53: 111-119.
40. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg* 2011; 115: 1248-1255.
41. Kostov H, Larsson PG, Røste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy? *Acta Neurol Scand Suppl* 2007; 187: 55-58.
42. Thammongkol S, Vears DF, Bicknell-Royle J, Nation J, Draffin K, Stewart KG, et al. Efficacy of the ketogenic diet: which epilepsies respond? *Epilepsia* 2012; 53: e55-e59.
43. Grooms LB, Pyzik PL, Turner Z, Dorward JL, Goode VH, Kossoff EH. Do patients with absence epilepsy respond to ketogenic diets? *J Child Neurol* 2011; 26: 160-165.
44. Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. *Health Technol Assess* 2005; 9: 1-157.

Related articles

Unalp A, Uran N, Hizli T, Ozturk A. Topiramate as a long-term therapy in children with refractory epilepsy. *Neurosciences* 2008; 13: 391-394.

Hammad AB, Diah El Deen OA, Massoud HMA, El Sawy MA. Clinical, genetic and neurophysiological approach to idiopathic epilepsy among Egyptian families. *Neurosciences* 2003; 8 (Suppl): 28.

Mohamed GF. Strategy of management of intractable epilepsy. *Neurosciences* 2008; 13 (Suppl): 44.

Hussein K, Khan S. Efficacy and safety of vagus nerve stimulation for intractable epilepsy at Riyadh Military Hospital: *A one-year follow up study*. *Neurosciences* 2008; 13 (Suppl): 45.