Juvenile Myoclonic Epilepsy Refractory to Treatment in a Tertiary Referral Centre

Gonçalo Cação [1], Joana Parra [2], Shahidul Mannan [3], Sanjay M. Sisodiya [3, 4], Josemir W. Sander [3, 4, 5]

1. Neurology Department, Centro Hospitalar do Porto, Largo do Prof. Abel Salazar, 4099-001 Porto, Portugal
2. Neurology Department, Centro Hospitalar Universitário de Coimbra, Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal
3. NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
4. Chalfont Centre for Epilepsy, Chalfont St Peter, Bucks, SL9 8ES, UK
5. Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 5, 2103SW Heemstede, Netherlands

Correspondence to:

Gonçalo Cação
Serviço de Neurologia - Centro Hospitalar do Porto,
Largo Professor Abel Salazar
4099-001 Porto, Portugal
Email – goncalo.cacao@gmail.com
Phone – +351 912 860 834

Word Count

Abstract: 250

Main text: 2229

References: 39

Box: 1

Table: 2

Figure: 1

Disclosure: GC, JP and SM have no conflicts to disclose. SMS has received fees for lectures, or institutional support, from GSK, Vitaflo, Nutricia, Eisai and UCB Pharma. JWS has received research

support and honoraria from UCB, Eisai, Bial and Janssen Cilag, which are involved in the manufacturing of antiepileptic drugs.

Funding: This work did not receive any specific funding.

Abstract

Introduction: Juvenile Myoclonic Epilepsy (JME) is an epileptic syndrome often regarded as one in which seizures are relatively easy to control. Not infrequently, however, individuals with JME require lifelong therapy to remain seizure-free and a few have refractory epilepsy. We ascertained a population with JME and characterized a refractory subgroup.

Material and Methods: We audited and reviewed clinical records of individuals diagnosed with JME identified via a sample of 6,600 individuals in a clinical database at a specialized epilepsy clinic at a tertiary referral center.

Results: We identified 240 people with a diagnosis of JME (146 females), with mean age at seizure onset 14.2 years (SD 4.5) and mean age at diagnosis 15.6 years (SD 4.9). Clinical phenotypes seen were classic JME phenotype (88%), childhood absence epilepsy evolving into JME (6%), JME with adolescent absences (4%) and JME with astatic seizures (2%). More than a quarter (28%) had a family history of epilepsy. The most commonly used AED was sodium valproate, in 78% of individuals, followed by levetiracetam (64%) and lamotrigine (55%). In the previous year, 47.5% were seizure-free. Using the ILAE definitions and considering NICE recommended AEDs for this syndrome, 121 individuals (50.4%) were identified as having refractory epilepsy.

Discussion: JME is often regarded as a benign epileptic syndrome but in this setting half of the individuals with JME have refractory epilepsy with only about a quarter of those seizure-free in the previous year. Despite some advances in the understanding of this syndrome, there is still much to do before we can offer all the best outcomes.

Highlights

- JME is often said to be benign but not infrequently people have refractory seizures
- Classic phenotype is the most frequent in refractory cases
- More than a quarter have a family history of epilepsy
- During the previous year, seizure freedom was only seen in about half of the cohort
- JME has a variable prognosis without clear markers to predict a refractory course

Key words:

Genetic epilepsies, clinical phenotypes, antiepileptic drugs

Main Text

1. Introduction

The International League against Epilepsy (ILAE) [1] fully recognized juvenile myoclonic epilepsy (JME) in 1985, almost 120 years after the first clinical report [2] and 30 years after it was described [3]. JME is defined by the ILAE [4] as an epilepsy syndrome, a subgroup of Genetic Generalised Epilepsies (GGE), characterised by myoclonic jerks (MJ), which occur in a fully conscious state and predominate in the upper limbs, usually on awaking. Absence and generalized tonic–clonic seizures (GTCS) may occur in 50-80% of individuals. In 2013, an international experts panel proposed two sets of criteria for JME diagnosis [5], both relying on a clear history of myoclonic jerks predominantly after awakening and an EEG with generalized epileptiform discharges supporting a diagnosis of idiopathic generalized epilepsy (Box 1). Clinical phenotypes in JME were reported in the first descriptions [6-8], but only later [9] was a classification proposed with four subgroups: classic JME, childhood absence epilepsy (CAE) evolving to JME, JME with adolescent absence and JME with astatic seizures (see Box 1).

Seizures in JME are often regarded as relatively easy to control. Not infrequently, however, individuals require lifelong therapy to remain seizure-free. A few present with refractory epilepsy, defined by the ILAE as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AED) schedules (whether as monotherapies or in combination) to attain sustained seizure freedom [10]. The UK National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis and management of epilepsies [11] included recommendations for the pharmacological treatment of JME. Sodium valproate was recommended as first-line treatment and lamotrigine, levetiracetam or topiramate were considered first-line if sodium valproate was unsuitable or not tolerated. If first-line treatments were ineffective or not tolerated, lamotrigine, levetiracetam, sodium valproate or topiramate should be offered as adjunctive treatment. If adjunctive treatment is ineffective or not tolerated, clobazam, clonazepam or zonisamide should be considered. Lastly, the guidelines emphasize that the use of carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin should be avoided as they may aggravate seizures.

We audited a large subsample of people with epilepsy at a tertiary epilepsy center to identify those with JME with a special focus on the treatment used, to assess adherence to the NICE guidelines.

2. Material and methods

We preformed a registered clinical audit to identify individuals with JME and to assess adherence to NICE guidelines regarding their treatment. We identified 1078 people with GGE from a subsample of 6,600 individuals with epilepsy using an outpatient registry. We then reviewed individual records to identify those with JME according to the ILAE definition [4]. Those of had failed two appropriate AEDs for the syndrome on the grounds of efficacy were considered refractory. Clinical and demographic data collected included sex, age at seizure onset, age at diagnosis, coexisting seizure types, seizures facilitators, clinical phenotypes (according to the 2006 [9] classification), past medical history and family history of epilepsy. Where available, EEG findings, brain imaging, neuropsychological and psychiatric evaluations were reviewed. Current and past treatments were reviewed along with seizure control over the previous years, allowing for identification of people with a refractory condition.

Data processing and statistical analysis was performed with Microsoft Excel 2013® and IBM SPSS (Statistical Package for the Social Sciences) V22.0®. Demographic and clinical characteristics were compared between refractory and non-refractory groups using the 2-tailed, Wilcoxon rank-sum test for continuous variables with a non-normal distribution and the Fisher exact test for categorical variables. A p value of < 0.05 was considered as statistically significant. No correction for multiple comparisons was performed as these were not consider an in view of the small number of multiple comparisons.

3. Results

We identified 1078 people diagnosed with GGE of whom240 met the criteria for JME and were included. Demographic and clinical characteristics are summarized in Table 1. Using the ILAE definition and NICE recommended AEDs for this syndrome, 121 individuals (50%) were identified as having refractory epilepsy. Table 2 characterises and compares the refractory group and the non-refractory group. The difference between the mean age at seizure onset and at diagnosis suggests a similar diagnostic delay of 1.4 years in both groups. Seizure types coexisting with myoclonus were convulsive seizures in 237 people (99%), absences in 98 (41%) and astatic seizures in 5 (2%).

Clinical phenotypes are described in Table 1 and 2, with the majority (88%) having classic JME, especially in the non-refractory group (96%). Other phenotypes were more prevalent in the refractory group. Sleep deprivation was described as a seizure precipitant by 102 people (43%), alcohol consumption by 44 (18%), photosensitivity by 33 (14%) and stress by 41 (17%). A family history of epilepsy was present in 67 people (28%), including in 38 first-degree relatives, of which 3 had JME.

Typical EEG findings were found in 192 people (80%), with photosensitivity present in 39 (20%) of these. Normal EEGs were recorded in 39 (16%) individuals, all of them on AED. EEG was not available in nine (done elsewhere). MRI brain imaging scans were performed in 216 people (90%)

and were normal in 179 (85%). The remaining showed non-specific white matter changes in 15 and incidental findings in the others, including: diffuse brain atrophy in 3, cerebellar atrophy in 3, arachnoid cyst in 2, developmental venous anomaly in 2 and pineal cyst in 1.

Neuropsychological evaluation was available in 75 individuals (31%), showing mild widespread dysfunction in 15 (20%), executive dysfunction in 12 (16%), verbal learning dysfunction in 11 (14.7%), verbal and non-verbal memory weakness in seven (9.3%), visual memory dysfunction in three (4%) and was normal in 27 (36%). We did not correlate cognitive performance and AEDs in use. Thirty people (12.5%) had psychiatric evaluation, which suggested anxiety in 14 (47%), depression in 12 (40%) and was normal in four (13%).

The most commonly used AED over the recorded course of the condition was sodium valproate (188 people; 78%), followed by levetiracetam (154; 64.2%), lamotrigine (133; 55%), clobazam (63; 26%), carbamazepine (62; 26%), zonisamide (59; 25%), topiramate (54; 23%), phenytoin (38; 16%), clonazepam (36; 15%), phenobarbital (21; 9%) and ethosuximide (15; 6%). Other AEDs used by 15 individuals in total included lacosamide, perampanel, gabapentin, primidone, acetazolamide, vigabatrin, pregabalin and sulthiame. Figure 1 shows past and current AEDs used. Two individuals had never taken AEDs. Seizure freedom with the first AED was seen in 41 (17%) individuals and in another 43 (18%) with the second AED. NICE non-recommended AEDs were used by 43 (18%) individuals, usually as adjunctive drugs. Forty-four of the 146 females were currently using sodium valproate (25 of childbearing age) and 60 had used this in the past. Amongst those on valproate, it was used as monotherapy in four and as part of a two AED regimen in eleven. The remaining were using valproate as part of a polytherapy regime mainly due to refractoriness.

In the previous year, 114 individuals (48%) were seizure-free, 30 (13%) had only MJ or absences and 84 (35%) also had convulsions. One died and 11 were lost to follow-up. On last follow-up, the majority (63%) of the non-refractory group was taking one AED, while 86% of the refractory group were taking two or more AEDs.

4. Discussion

JME is often regarded as a benign epileptic syndrome, with some reports even suggesting that some individuals are seizure-free without AEDs [12]. In our sample, however, about half of individuals have refractory epilepsy, suggesting a possible referral bias as the setting is a major tertiary referral centre, which is more likely to attract referral of more refractory cases.

Females were more prevalent in both groups. Age of onset was slightly higher in the easy-to-control group but diagnostic delay was similar, suggesting that the diagnosis in people with refractory disease is does not pose a more difficult diagnostic challenge. In our sample we found that, although

the classic clinical phenotype was the most prevalent in both groups, other phenotype subgroups were more prevalent in the refractory group. The phenotype difference between groups was statistically significant. It was reported previously[9] that 72% of people presented with the classic subtype with over half of these seizure-free, a fifth had CAE evolving to JME with 7% seizure-free, 7% JME with adolescent absence with 56% seizure-free and 3% JME with astatic seizures with 62% seizure-free. Others also observed worse seizure control in those with previous CAE [13, 14].

Only small non-significant differences were seen between groups regarding a family history of epilepsy. This was present in more than a quarter of individuals, but differences in the presence or absence of epilepsy in the family were not significant between the refractory and non-refractory group. This supports previously reported studies suggesting an underlying genetic predisposition to JME [15-19].

EEGs finding were not different between groups. Abnormal MRI findings were interpreted as incidental and group differences were not significant. Overall, imaging studies in JME are normal, but advanced neuroimaging studies suggests functional and structural abnormalities in the frontal cortex and thalamus [16, 20]. This would be in accordance with some evidence of thalamo-frontocortical network dysfunction [16, 21-24], as a putative pathophysiological mechanism for JME. There seems to be a subnetwork of hyperconnectivity, involving primary motor, supplementary motor, parietal and subcortical regions, which may contribute to myoclonic seizure generation [25-27]. The presence of altered motor system activation and functional connectivity in unaffected JME siblings demonstrates that this is not medication or seizure-related, but may constitute a genetically determined JME endophenotype [16, 18].

In our cohort, neuropsychological evaluation profiles often shown mild widespread malfunctioning and executive dysfunction, in concordance with previous reports that people with JME have executive and attention issues characterized by deficits in mental flexibility, planning, concept formation, inhibitory control, attentional processes, memory, visuospatial function and verbal fluency [28-31]. In our sample, there were no group differences on neuropsychological evaluation. Neuropsychiatric evaluation, although infrequently performed, suggested that anxiety and depression are relatively common in these individuals, significantly more in the refractory group. As not all individuals were evaluated and the impact of polymedication was not assessed, conclusions about neuropsychological and neuropsychiatric evaluations are challenging.

Significantly, more people in the refractory group are on poly-therapy and this should not come as surprise. Nice recommended AEDs are among the most used in this cohort as over three-quarters using them. About a fifth were using AEDs outside the NICE recommendations. The SANAD study [32] compared valproate, lamotrigine and topiramate in people with generalised seizures. The JME subgroup was not specifically addressed but it was concluded that sodium valproate should remain first line

treatment for most people with idiopathic generalised epilepsy or seizures that are difficult to classify, whereas lamotrigine and topiramate should generally be avoided due to the inferior efficacy of lamotrigine and the inferior tolerability of topiramate [32]. Conversely, other studies support the use of topiramate [33] and lamotrigine [34] in people with JME. The most reasonable treatment path in these individuals is to follow NICE guidelines. For women, in view of its potential teratogenicity, valproate should only be a last resort option.

Despite the type and number of AEDs used in different combination, only a quarter of the refractory group were seizure-free in the previous year, compared with 71% of the non-refractory group. Overall, 48% of individuals were seizure-free in the previous year, considerably lower than reported in other studies [12, 35-38], which, as stated before, is probably due to the higher ratio of refractory epilepsy in our sample. Despite recent advances in the understanding of this syndrome, there is still much needed before we will be able to offer the best outcome to all as it has been shown that early seizure freedom improves social adjustment and occupational integration and is associated with a better quality of life [39].

A major limitation of the exercise is its retrospective nature and dependency on the accuracy and completeness of the existing medical records. Some people with JME amongst those diagnosed with GGE may have been missed. Seizure frequency data are often problematic in such retrospective exercises and this makes it a challenge to establish an exact correlation between AED changes and changes in seizure control but we have attempted deal with this in a pragmatic way. AED adherence was difficult to assess and, this could lead to some cases being "pseudo-refractory". The sample was also drawn from a population in a tertiary referral centre, including incident and prevalent cases, which may have biased this exercise towards the more refractory end of the clinical spectrum of JME. The strengths of this exercise is the size of the cohort with a thorough comparison of refractory and non-refractory groups, which adds information to the clinical ascertainment of this entity.

5. Conclusion

JME is still a challenging condition, with variable prognosis and without clear markers to predict a refractoriness. The challenge of seizure freedom is even greater in this syndrome than in other epilepsy syndromes due to the psychological profile of these individuals may led to difficulties in treatment adherence. Prospective multicenter studies of an incident population with refractory JME will probably bring more information on this common condition.

Acknowledgements

This work as carried out at University College London Hospitals/University College London Comprehensive Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. JWS receives research support from the Dr Marvin Weil Epilepsy Research Fund and the UK Epilepsy Society. The authors are grateful to Dr Gail S Bell for critically reviewing the manuscript.

References:

1. Commission on Classification and Terminology of the International League against Epilepsy. Proposal for classification of epilepsies and epileptic syndromes. Epilepsia. 1985;26:268-78
2. Herpin T. Des acces incomplets d'epilepsie. Bailliere; Paris: 1867. p. 162-70
3. Janz D, Christian W. Impulsiv petit mal. Dtsch Z Nervenheilkd 1957;176:346–86
4. Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and epilepsy: report of the ILAE task force on classification and terminology. Epilepsia 2001; 42: 796–803
5. Kasteleijn-Nolst Trenité DG, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, Lerche H, Camfield C, Baykan B, Feucht M, Martínez-Juárez IE, Duron RM, Medina MT, Rubboli G, Jerney J, Hermann B, Yacubian E, Koutroumanidis M, Stephani U, Salas-Puig J, Reed RC, Woermann F, Wandschneider B, Bureau M, Gambardella A, Koepp MJ, Gelisse P, Gurses C, Crespel A, Nguyen-Michel VH, Ferlazzo E, Grisar T, Helbig I, Koeleman BP, Striano P, Trimble M, Buono R, Cossette P, Represa A, Dravet C, Serafini A, Berglund IS, Sisodiya SM, Yamakawa K, Genton P. Consensus on diagnosis and management of JME: From founder's observations to current trends. Epilepsy Behav. 2013 Jul;28 Suppl 1:S87-90.
6. Janz D. Epilepsy with impulsive petit mal (juvenile myoclonic epilepsy). Acta Neurol Scand 1985; 72: 449–59
7. Tsuboi T. Primary generalized epilepsy with sporadic myoclonias of myoclonic petit mal type. Stuttgarg: Thieme; 1977
8. Mai R, Canevini MP, Pontrelli V, Tassi L, Bertin C, Di Marco C, et al. L'epilessia mioclonica giovanile di Janz: analisi prospettica di un campione di 57 pazienti. Boll Lega It Epil 1990; 70/71: 307–9
9. Martínez-Juárez IE, Alonso ME, Medina MT, Durón RM, Bailey JN, López-Ruiz M, Ramos-Ramírez R, León L, Pineda G, Castroviejo IP, Silva R, Mija L, Perez-Gosiengfiao K, Machado-Salas J, Delgado-Escueta AV. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. Brain. 2006 May;129(Pt 5):1269-80

10. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy. Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia.

11. National Institute for Health and Clinical Excellence, 2012 Epilepsies: diagnosis and management. NICE guidelines [CG137]: London Available at: https://www.nice.org.uk/guidance/cg137.

12. Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology. 2009 Sep 29;73(13):1041-5.

13. Wirrell E, Camfield C, Camfield P, Dooley J. Prognostic significance of failure of the initial antiepileptic drug in children with absence epilepsy. Epilepsia. 2001 Jun;42(6):760-3

14. Guaranha MS, Filho GM, Lin K, Guilhoto LM, Caboclo LO, Yacubian EM. Prognosis of juvenile myoclonic epilepsy is related to endophenotypes. Seizure. 2011 Jan;20(1):42-8

15. Schmitz B, Yacubian EM, Feucht M, Hermann B, Trimble M. Neuropsychology and behavior in juvenile myoclonic epilepsy. Epilepsy Behav. 2013 Jul;28 Suppl 1:S72-3

16. Wandschneider B, Thompson PJ, Vollmar C, Koepp MJ. Frontal lobe function and structure in juvenile myoclonic epilepsy: a comprehensive review of neuropsychological and imaging data. Epilepsia. 2012 Dec;53(12):2091-8

17. Iqbal N, Caswell H, Muir R, Cadden A, Ferguson S, Mackenzie H, Watson P, Duncan S. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: An extended study. Epilepsia. 2015 Aug;56(8):1301-8

18. Wandschneider B, Centeno M, Vollmar C, Symms M, Thompson PJ, Duncan JS, Koepp MJ. Motor co-activation in siblings of patients with juvenile myoclonic epilepsy: an imaging endophenotype? Brain. 2014 Sep;137(Pt 9):2469-79

19. Cossette P. Channelopathies and juvenile myoclonic epilepsy. Epilepsia. 2010 Feb;51Suppl 1:30-2

20. Anderson J, Hamandi K. Understanding juvenile myoclonic epilepsy: contributions from neuroimaging. Epilepsy Res. 2011 May;94(3):127-37

21. Kim SH, Lim SC, Kim W, Kwon OH, Jeon S, Lee JM, Shon YM. Extrafrontal structural changes in juvenile myoclonic epilepsy: a topographic analysis of combined structural and microstructural brain imaging. Seizure. 2015 Aug;30:124-31

22. Alhusaini S, Ronan L, Scanlon C, Whelan CD, Doherty CP, Delanty N, Fitzsimons M. Regional increase of cerebral cortex thickness in juvenile myoclonic epilepsy. Epilepsia. 2013 Sep;54(9):e138-41

23. Kim JB, Suh SI, Seo WK, Oh K, Koh SB, Kim JH. Altered thalamocortical functional connectivity in idiopathic generalized epilepsy. Epilepsia. 2014 Apr;55(4):592-600.

24. Kim JH, Suh SI, Park SY, Seo WK, Koh I, Koh SB, Seol HY. Microstructural white matter abnormality and frontal cognitive dysfunctions in juvenile myoclonic epilepsy. Epilepsia. 2012 Aug;53(8):1371-8

25. O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, Duncan JS, Koepp MJ, Richardson MP. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. Brain. 2012 Dec;135(Pt 12):3635-44.

26. Focke NK, Diederich C, Helms G, Nitsche MA, Lerche H, Paulus W. Idiopathic-generalized epilepsy shows profound white matter diffusion-tensor imaging alterations. Hum Brain Mapp. 2014 Jul;35(7):3332-42

27. Caeyenberghs K, Powell HW, Thomas RH, Brindley L, Church C, Evans J, Muthukumaraswamy SD, Jones DK, Hamandi K. Hyperconnectivity in juvenile myoclonic epilepsy: a network analysis. NeuroimageClin. 2014 Nov 27;7:98-104

28. Seneviratne U, Cook M, D'Souza W. Focal abnormalities in idiopathic generalized epilepsy: a critical review of the literature. Epilepsia. 2014 Aug;55(8):1157-69.

29. Loughman A, Bowden SC, D'Souza W. Cognitive functioning in idiopathic generalised epilepsies: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2014 Jun;43:20-34

30. Valente KD, Rzezak P, Moschetta SP, de Vincentiis S, Coan AC, Guerreiro CA. Delineating behavioral and cognitive phenotypes in juvenile myoclonic epilepsy: Are we missing the forest for the trees? Epilepsy Behav. 2016 Jan;54:95-9

31. Cevik N, Koksal A, Dogan VB, Dirican AC, Bayramoglu S, Ozturk M, Baybas S. Evaluation of cognitive functions of juvenile myoclonic epileptic patients by magnetic resonance spectroscopy and neuropsychiatric cognitive tests concurrently. Neurol Sci. 2015 Nov 24

32. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007 Mar 24;369(9566):1016-26.

33. Park KM, Kim SH, Nho SK, Shin KJ, Park J, Ha SY, Kim SE. A randomized open-label observational study to compare the efficacy and tolerability between topiramate and valproate in juvenile myoclonic epilepsy. J Clin Neurosci. 2013 Aug;20(8):1079-82

34. Machado RA, García VF, Astencio AG, Cuartas VB. Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial. Seizure. 2013 Dec;22(10):846-55.

35. Höfler J, Unterberger I, Dobesberger J, Kuchukhidze G, Walser G, Trinka E. Seizure outcome in 175 patients with juvenile myoclonic epilepsy--a long-term observational study. Epilepsy Res. 2014 Dec;108(10):1817-24.

36. Baykan B, Altindag EA, Bebek N, Ozturk AY, Aslantas B, Gurses C, Baral-Kulaksizoglu I, Gokyigit A. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. Neurology. 2008 May 27;70(22 Pt 2):2123-9.

37. Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, Runge U. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25-63 years of follow-up. Epilepsia. 2012 Aug;53(8):1379-86.

38. Senf P, Schmitz B, Holtkamp M, Janz D. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. Neurology. 2013 Dec 10;81(24):2128-33.

39. Schneider-von Podewils F1, Gasse C, Geithner J, Wang ZI, Bombach P, Berneiser J, Herzer R, Kessler C, Runge U. Clinical predictors of the long-term social outcome and quality of life in juvenile myoclonic epilepsy: 20-65 years of follow-up. Epilepsia. 2014 Feb;55(2):322-30