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Review

Long-term prognosis of juvenile myoclonic epilepsy: A systematic review searching for sex differences

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ABSTRACT

Purpose: Juvenile myoclonic epilepsy (JME), like other forms of idiopathic generalized epilepsy, shows a marked female predominance. However, few studies have specifically addressed the role of sex in its long-term prognosis. We performed a systematic review of the literature relevant to JME prognosis, focusing on sex-based differences in prognostic factors and outcome.

Methods: A comprehensive literature search of the PubMed and Scopus databases was performed, considering all articles up to April 2020 in which long-term prognosis in JME had been explored and sex differences in outcome or prognostic factors were specified.

Results: We included 25 articles published between 1984 and 2020. Sex differences in epilepsy outcome were explored by 21 of the 25 studies, but only three reported different outcomes in male vs female patients. All three found female sex to be associated with a later response to antiseizure medications, worse seizure control, and a higher risk of relapse in their entire study samples, which included JME patients. Eight studies found sex-based differences in possible predictors of long-term outcome: prolonged epileptiform EEG runs and the presence of eye closure sensitivity, both more frequent in women, were factors possibly linked to a poorer prognosis, as were praxis induction and generalized EEG asymmetric changes, which instead were more common in men. Valproate use, more frequent in men, was associated with a better outcome.

Conclusion: Most studies do not highlight sex differences in JME prognosis. However, some sex specificities do emerge, especially with regard to particular reflex traits and EEG abnormalities. Finally, sex may condition therapeutic choices, and thus have a possible impact on long-term outcome.

1. Introduction

According to epidemiological studies, the incidence and prevalence rates of epilepsy are slightly higher in men than in women [1]. This difference could be due to various causes but it seems to be explained by sex differences in the prevalence of the most common risk factors for

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epilepsy [1].

However, the opposite trend has been observed in patients with idiopathic generalized epilepsy (IGE), a group of epilepsy syndromes currently referred to also as genetic generalized epilepsies (GGE) [2], with a female predominance being reported in juvenile myoclonic epilepsy (JME), childhood absence epilepsy, and juvenile absence epilepsy patients [3–5].

In JME, in particular, females account for 60 % of all cases [3–7].

The reasons for this marked difference are not well established, although predisposing genes and the influence of sex hormones on brain circuit excitability have been suggested to play a role [8,9].

Moreover, some differences in the clinical features of JME have been reported between the two sexes, especially with regard to reflex traits, with photosensitivity being more frequent among female patients [10] and praxis induction (PI) more frequently reported in males [11].

However, few studies to date have specifically addressed the influence of sex on the long-term prognosis of the disease.

The long-term prognosis of JME is still considered a critical issue, given that a considerable number of patients relapse after treatment withdrawal [12].

Many attempts have been made to investigate the long-term prognosis of JME, focusing on factors associated with a worse outcome. Indeed, a recent meta-analysis highlighted a series of clinical variables linked to refractory JME, namely, having three different seizure types, absence seizures, psychiatric comorbidities, an earlier age at seizure onset, a history of childhood absence epilepsy, and praxis-induced seizures. In this study, female sex was associated with a worse prognosis but this result did not reach statistical significance [13].

Against this background, the aim of our study was to perform a systematic review of the literature dealing with the long-term prognosis of JME, focusing on differences in prognostic factors and long-term outcome between male and female patients.

2. Material and methods

2.1. Search strategy and study selection process

We carried out a comprehensive literature search of the PubMed and Scopus research databases, using the following keywords: “juvenile myoclonic epilepsy” AND (“prognosis” OR “outcome”). The search was conducted with no restriction on article publication date, and all results up to April 2020 were included. After removal of duplicates, the titles, abstracts and/or full texts of the remaining articles were screened and assessed for eligibility by two reviewers (LG, GM), working independently. Disparities were resolved by discussion.

Articles were included if they met the following criteria:

- Articles in English, Italian, Spanish or French.
- Articles reporting studies that had explored long-term prognosis in patients with JME, and in which sex differences in outcome or prognostic factors were specified.
- Studies involving patients with all types of IGE, or with mixed populations, in which data on JME were clearly distinct from those on other epilepsy types.

We considered studies with any age range. Among different publications including the same study population, the one with the most comprehensive data was selected.

The reference sections of all retrieved articles were examined for additional sources of data.

We excluded conference proceedings, reviews and single case reports.

2.2. Data extraction

The following data, drawn from the selected literature, were entered, for each study, in an ad-hoc created database: the first author and the year of publication, the country in which the study was performed, the language of the article, the study design, the diagnostic criteria used, the study period, the study sample size, the age range of the enrolled sample, the sex ratio reported, the years of follow-up, the seizure-free time defining seizure freedom in each study, the seizure-freedom rate as well as the relapse rate after discontinuation of antiseizure medications (ASMs), and the reported sex differences in outcome and prognostic factors, considering also the differences in ASMs schedules, when specified. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Supplement 1).

2.3. Quality assessment

The quality of the included studies was evaluated using the Quality In Prognosis Studies assessment tool (QUIPS), which was specifically designed to assess the risk of bias (RoB) in prognostic studies [14]. The study attrition subscale was not used as it was not always applicable. If all the domains were classified as having a low RoB or included just one with a moderate RoB, then the article was defined “low RoB”; if one or more domains were classified as having a high RoB or >3 as having a moderate RoB, then the article was defined “high RoB”. All papers falling between these criteria were defined “moderate RoB”. The RoB of the analyzed studies was evaluated independently by two of the study investigators (LG and GM). This parameter was evaluated considering the purpose of our review, and regardless of the aims of the single studies.

3. Results

3.1. Characteristics of the studies

The literature search of the two databases yielded a total of 558 articles (Fig. 1). After removal of duplicates and application of the inclusion and exclusion criteria, a total of 23 articles remained for inclusion in the study; to these, a further two studies, identified through searching of the references of the eligible articles, were then added (Table 1 [11,15–38] and Fig. 1).

The 25 articles included in the qualitative synthesis were published between 1984 and 2020 (Table 1 [11,15–38]).

All were carried out in hospital-based settings. The majority (11, 44 %) were performed in Europe [17,20–22,24,25,27,28,33,35,38], while seven (28 %) were performed in Asia [16,18,23,26,30,32,37], four (16 %) in South America [11,15,19,29], two (8 %) in North America [31,34], and one (4 %) in Africa [36]. All except one, written in Spanish [15], were in English.

Of the 25 articles analyzed, 20 included only patients with JME [11,15–27,29,32,35–38], three of them focusing on specific endophenotypes such as eye closure sensitivity (ECS) [19,26] and PI [11]. Among the other five studies [28,30,31,33,34], three included IGE samples [28,30,33], one specifically addressing photosensitive IGE [30], one enrolled patients with different types of adolescent-onset epilepsy, both focal and generalized [31], and the other included patients with pattern-sensitive epilepsy [34].

The study samples ranged from 13 [31] to 240 patients [20].

The duration of follow-up in years was specified, or could be calculated, in 21 of the 25 studies (84 %) [11,15–19,21–32,34–36]. The years of follow-up ranged widely, from 1 [15,17] to 47.9 years [18].

As regards the quality of the analyzed studies, 12 of the 25 (48 %) were defined “low RoB” [15,16,21,23,25,27–29,32–34], 10 (40 %) “moderate RoB” [17–20,22,24,26,31,35,36], and 3 (12 %) “high RoB” [30,37,38] (Supplementary Table 1).

3.2. Sex ratio

In all but three of the studies [31,36,37], it was possible to estimate

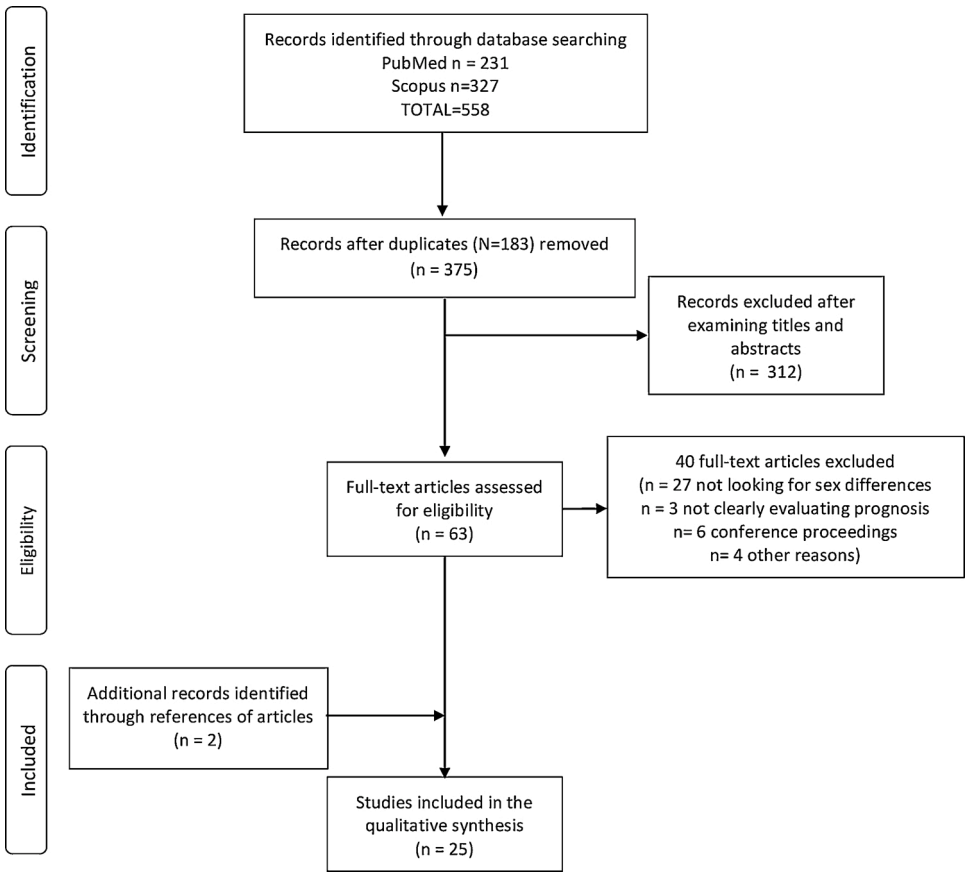

Fig. 1. Flowchart showing the study selection procedure.

the sex ratio of patients with JME. The lowest female-to-male (F/M) ratio reported was 0.96/1 and the highest 2.5/1; the mean was 1.47/1. However, in two studies [33,34], this ratio could be calculated only for the whole sample of IGE patients, and not for JME patients alone (Table 2).

3.3. Sex differences in outcome and relapse risk

Sex differences in epilepsy outcome were explored by 21 of the 25 studies [15–18,20–35,37] (Table 2), with 18 (85.7 %) finding no differences [15–18,20,21,23–27,29,30,32,21–35,37].

Of these 18 studies, 13 specifically addressed JME [15,16,18,20,21,23,25–27,29,32,35,37], two studies considered JME patients as subgroups of a cohort of IGE patients [33] and of a cohort with pattern-sensitive epilepsy [34], and another study focused solely on photosensitive JME subjects [30]. Regarding response to ASMs, the study by Syvertsen et al. found no sex differences in the rates of ASM withdrawal and subsequent relapse between male and female patients with JME [17], while Jović et al. [24] showed that sex was not associated with drug resistance.

Only three studies [22,28,31] detected sex-related differences in outcome.

Specifically, Chowdhury and Brodie [22] retrospectively included 186 JME patients with a minimum of two years of follow-up; of these, 42 % were males and 58 % were females (sex ratio = 1.4/1). While overall remission rates (93.5 % vs 89.8 % respectively) as well as the response to the first ASM schedule did not differ, more males than females (81 % vs 17 %) achieved an earlier remission, i.e. responded to their second ASM schedule, while women remitted only with a third/fourth ASM schedule.

To evaluate the rate of relapse after discontinuation of ASMs, Pavlovic et al. [28] prospectively enrolled 59 IGE patients, 22 females (37.3 %) and 37 males (62.7 %), with an established clinical remission of at least two years prior to ASM withdrawal and a minimum follow-up of two years after it. Among these patients, only 17 (28.8 %) were affected by JME. Of these, 7 were excluded because of ASM reintroduction due to the reappearance of EEG epileptiform abnormalities, and the remaining 10 (6 females and 4 males) had a relapse after discontinuation of ASMs. Female sex was found to be a predictor of relapse on univariate analysis (HR = 2.59; 95 %CI = 1.21–5.21; p = 0.01), but only in the whole IGE sample, in which 62.1 % of females vs 33.3 % of males had a relapse.

Simard-Tremblay et al. [31], in their study, retrospectively included subjects with adolescent-onset epilepsy, both focal and generalized, from three different clinical settings (hospital-based ambulatory clinic, hospital-based private neurology office, and suburban private pediatric neurology clinic). Sixty-five adolescents were included (35 males [53.8 %] and 30 females [46.2 %]). Of the 39 subjects with IGE, 13 (20 %) had a diagnosis of JME. A diagnosis of JME was associated with the need to continue ASMs at the last follow-up visit. Moreover, female sex was found to be associated with worse seizure control in the entire sample, with only 9 of the 30 females (30 %) found to be off medication at the last follow-up.

3.4. Sex differences in prognostic factors and ASMs schedules

Only eight studies analyzed sex differences in factors that may predict long-term outcome of JME [11,16,18,19,21,22,36,38] (Table 2).

In a retrospective study that included 215 patients with JME, Gürer et al. [16] analyzed long-term outcome and responses to different doses of VPA (low doses <750 mg/day vs high doses >750 mg/day). They found that remission was achieved with lower doses of VPA in females than in males. Moreover, analyzing EEG findings, they found generalized asymmetric changes to be more common in the refractory group and significantly more frequent in males.

Landmark et al. [38], in a study of 90 patients with JME (54 females

Table 1
Selected studies characteristics.

First author/year	Country	Study design	Diagnostic criteria	Study years	Study sample	Follow-up in years	Age range (years)	Time to define seizure-freedom	Seizure freedom rate	Relapse rate
Sánchez-Zapata 2019	Colombia	Retrospective cohort	ILAE 1989	2014–2016	145	1	21–38	1 year	64.8 64.8 %	NS
Gürer 2019	Turkey	Retrospective cross-sectional	NS	NS	215	9.98	14–59	2 years	61.4 %	15.4 %
Landmark 2019	Norway	Retrospective cohort	Consensus JME 2013	2016-2018	90	NS	14–39	1 year	33 %	NS
Syvertsen 2019	Norway	Retrospective cohort	Consensus JME 2013	1999–2013	87	1	Mean: 25.7	NS	NS	65.7 %
Zhang 2019	China	Prospective cohort	ILAE 2001	2012–2014	105	47.9 ± 7.2 (median)	16–41	1–3-5 years	64.8 %–29.5 % - 14.6 %	NS
Uchida 2018	Brazil	Prospective cohort	NS	NS	22 with ECS 20 without	8.21 ± 5	Mean: 28.1 with ECS 32.9 without	NS	18.2 % with ECS - 45 % without ECS	NS
Cação 2018	UK	Retrospective cohort	ILAE 2001	NS	240	NS	Mean: 38 refractory 39 non-refractory	1 year	47.5 %	NS
Arntsen 2017	Norway	Retrospective cohort	ILAE 1989	1992–2012	40	31.7[†]	35–81	5 years	52.5 %	NS
Chowdhury and Brodie 2016	UK	Retrospective cohort	NS	1982–2012	186	14 (median) (2–32)	NS	1 year	92 %	60.7 %
Uchida 2015	Brazil	Prospective cohort	NS	NS	20 with PI 25 without	7.82	30.5 with PI 33.4 without	NS	10 % with PI – 40 % without PI	NS
Asadi-Pooya 2014	Iran	Prospective cohort	NS	2008–2012	116	2.9[†]	Mean: 24.9 refractory 23.1 non-refractory	1 year	58.6 %	NS
Jović 2014	Serbia	Retrospective cohort	ILAE 1989	1987–2008	87	13.3 ± 5.8	17.5–43.5	5 years	77 %	64.7 %
Syvertsen 2014	Norway	Retrospective cohort	ILAE 1989	1992–2012	40	>20	35–81	5–10 years	52.5 %–32.5 %	42.8 %
Güveli 2013	Turkey	Retrospective cohort	ILAE 1989	NS	76	8.7[†]	NS	good prognosis NS	64.5 %	NS
Senf 2013	Germany	Retrospective cohort	ILAE 1989	NS	66	44.6 ± 13.7	31–84	5 years	59.1 %	7.1 %
Pavlovic 2011	Serbia	Prospective cohort	ILAE 1989	2001–2009	10	3 (median) (2–10)	11–36[**]	2 years after ASM withdrawal	NS	100 %
Guaranha 2011	Brazil	Prospective cohort	ILAE 1989	NS	65	5.72 ± 1.91	Mean: 24.40	2 years	38.5 %	NS
Demirkaya 2009	Turkey	Retrospective cohort	NS	Until 2007	24	9 (median) (2–22)	14–63	NS	37.5 %	NS
Simard-Tremblay 2009	Canada	Retrospective cohort	ILAE 2001	1991–2006	13	3.1 for all sample	NS	1 year (excellent seizure control)	84.6 %	NS
Baykan 2008	Turkey	Retrospective/ Prospective cohort	ILAE 1989	1972–2006	48	19.6 ± 5.7	Mean: 39.9	5 years	27.1 %	20 %
Mohanraj 2007	UK	Prospective cohort	ILAE 1981–1989	1981–2001	55	NS	NS	1 year	73 %	7 %
Radhakrishnan 2005	USA	Retrospective cohort	ILAE 1989	1950–1999	14	16.6 ± 12.5[**]	12–72.4	5 years[**]	45.5 %	NS
Gelisse 2001	France	Retrospective cohort	ILAE 1989	1981–1998	155	13.5 ± 9.9	15–70	NS	74.8 %	NS
Panayiotopoulos 1994	Saudi Arabia	Prospective cohort	NS	NS	66 (50)[*]	5	8–40	3 years	88 %	81.8 %
Matsuoka 1992	Japan	Retrospective cohort	NS	NS	32	NS	NS	NS	68 %[‡]	NS

UK, United Kingdom; USA, United States of America; ILAE; International League Against Epilepsy; NS, not specified; JME, juvenile myoclonic epilepsy; ASM, anti-seizure medication; ECS, eye closure sensitivity; PI, praxis induction.

[*] Only 50 patients had a follow-up >3 yrs, so the results refer to those 50 patients; the authors report rare myoclonias in ten of the patients included in the seizure-free group.

[**] For the entire sample. [†] Calculated by the authors.

[‡] This rate refers to myoclonic seizures alone.

Table 2
Sex differences in outcome or in prognostic factors in the selected studies.

First author/year	Female to male ratio	Sex differences in outcome	Sex differences in prognostic factors	Sex difference in ASMs schedules and relation to prognosis
Sánchez-Zapata 2019	1.5|1	No sex differences in outcome	NS	NS
Gürer 2019	1.3|1	No sex differences in outcome	Asymmetric EEG alterations, associated with drug-refractory group and significantly more common in men	No significant sex difference in first-line treatment options; lower mean VPA dose during remission in females
Landmark 2019	1.5|1	NS		VPA, associated with remission, mostly used in males; females are more frequently prescribed LTG and LEV as well as other monotherapies; more females than males off-medications; poor adherence not significantly associated with gender
Syvertsen 2019	1.3|1	No sex differences in ASM withdrawal and relapse	NS	NS
Zhang 2019	1.2|1	No sex differences in outcome		Valproate, more effective on GTCSs, most commonly used in males; more females than males with LEV monotherapy; trend of lower rates of SF in patients receiving LEV vs VPA monotherapy
Uchida 2018	2.5|1	NS	Female predominance of ECS, linked to a worse outcome	NS
Cação 2018	1.5|1	No sex differences in outcome	NS	NS
Arntsen 2017	1.7|1	No sex differences in outcome	Prolonged epileptiform EEG runs, associated with a worse prognosis, and more frequent in women	All patients exposed to VPA with the exception of 4 females
Chowdhury and Brodie 2016	1.4|1	Earlier ASM response in males		Lower use of VPA in females; men less likely to receive LTG e LEV as first ASM; similar proportion in males and females of drugs other than VPA, LTG and LEV
Uchida 2015	0.9|1	NS	Male predominance of PI, associated with a worse outcome	NS
Asadi-Pooya 2014	2|1	No sex differences in outcome	NS	Treatment strategy of the authors was to prescribe valproate for males and lamotrigine for females as first ASM
Jović 2014	1.3|1	Sex not associated with drug resistance	NS	NS
Syvertsen 2014	1.5|1*	No sex differences in outcome	NS	All patients exposed to VPA with the exception of 3 females
Güveli 2013	2.2|1	No sex differences in outcome	NS	NS
Senf 2013	1|1	No sex differences in outcome	NS	NS
Pavlovic 2011	1.5|1	Female sex predicted relapse at univariate analysis*	NS	NS
Guaranha 2011	1|1	No sex differences in outcome	NS	NS
Demirkaya 2009	2.|41	No sex differences in outcome in photosensitive JME	NS	NS
Simard-Tremblay 2009	NS	Female sex associated with worse seizure control *	NS	NS
Baykan 2008	1.5|1	No sex differences in outcome	NS	NS
Mohanraj 2007	1.2|1*	No sex differences in outcome*	NS	NS
Radhakrishnan 2005	1.4|1*	No sex differences in outcome*	NS	NS
Gelisse 2001	1.5|1	No sex differences in outcome	NS	NS
Panayiotopoulos 1994	NS	NS	Early-onset absences in women, late-onset absences in men	NS
Matsuoka 1992	NS	No sex differences in outcome	NS	NS

NS, not specified; JME, juvenile myoclonic epilepsy; ASM, antiseizure medication; ECS, eye closure sensitivity; PI, praxis induction; VPA, valproate; GTCSs, generalized tonic-clonic seizures.
* In the entire sample.

and 36 males), retrospectively evaluated outcome in response to different ASMs. They discovered a differential use of ASMs: two-thirds of VPA users were males, while other ASMs were used more frequently by females than by males. The majority of patients obtaining remission from generalized tonic-clonic seizures (GTCSs) were on VPA at the last follow-up.

Zhang et al. [18], in a sample comprising 105 prospectively enrolled JME patients, found that VPA monotherapy was more effective on GTCSs, more commonly used in men than women (37 vs 3), and did not affect the remission rate, which was comparable between the two sexes.

Similarly, in the work by Chowdhury and Brodie [22], overall, more male (53 %) than female (47 %) patients received VPA as their first ASM, and VPA accounted for 44 % of all ASMs given to male patients and only 31 % of all ASMs given to female patients. As reported above, the males in their study achieved an earlier remission than the females, and the difference was significant.

Arnsten et al. [21] retrospectively evaluated 40 JME patients, and reported no sex differences in outcome. However, they found that prolonged (≥3 s) epileptiform EEG runs were more frequent in women than in men, and that they were associated with persistent seizures at the last follow-up.

Uchida et al. [19], comparing the long-term prognosis of JME patients with and without ECS, found a female predominance (81.8 % vs 19.2 %) of this reflex trait that, in their study, was found to be associated with a worse outcome.

The same authors, in a prospective cohort [11], compared 20 JME subjects with PI with 25 subjects without any reflex trait. PI was more frequent among males (60 % vs 40 %), and this trait was associated with reduced response to ASMs at follow-up.

Panayiotopoulos et al. [36] observed a female predominance of early-onset absence seizures in a prospective cohort of 65 JME patients, while late-onset absences were more frequent in males with an unknown impact on prognosis. Finally, in the cohort studied by Syvertsen et al. [25], all three patients with persistent seizures and a history of absence epilepsy evolving to JME were females.

4. Discussion

JME is a heterogeneous and complex syndrome, belonging to the category of IGE, which is "characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms" [39]. Although usually well controlled by ASMs, seizures in JME patients tend to relapse after drug discontinuation [27,40]. Long-term prognosis of the disease thus remains a controversial issue, and this clearly has implications both for clinicians and for patients. Even though a female predominance in JME has been recognized ever since the first descriptions of the condition by Dieter Janz [41], sex-related features associated with its long-term outcome and sex differences in possible prognostic factors have rarely been investigated. The identification of sex-related prognostic aspects would constitute a crucial advance with hugely important therapeutic implications, especially given the current restrictions on the use of VPA in female populations [42].

The 25 studies that met the criteria for inclusion in our systematic review of the literature proved to be heterogeneous in terms of study design, samples, years of follow-up, and definition of seizure freedom (in terms of seizure-free time). In addition, some studies investigated the entire IGE category, including JME as a subgroup, while others focused on specific endophenotypes within the syndrome.

Moreover, as is often the case with retrospective studies, it was challenging to achieve an accurate evaluation of ASM schedules, which is a critical aspect when analyzing long-term outcome in epilepsy.

In line with a recent meta-analysis, in which female gender was not identified among the significant risk factors for refractory JME [13], the vast majority of the analyzed studies, regardless of their strength of evidence, did not show sex differences in the long-term outcome of JME. Conversely, the studies that investigated the entire IGE category [28,31] seemed to show a trend towards a negative outcome for women. The authors attributed this finding in part to the female prevalence in their samples, but also to the possible negative effect of female hormonal variations in terms of their influence on neuronal excitability and response to ASMs.

In JME, VPA is widely recognized to be highly effective in controlling seizures [22], even though recent controlled trials show a comparable efficacy of newer ASMs [43]. This aspect must be kept in mind when evaluating sex-related prognosis, since the decreased use of VPA in girls and women of childbearing potential, linked to the drug's teratogenic effects [44], might have repercussions on the disease outcome. Indeed, the choice of alternative treatments for women of childbearing potential, and in particular in those with IGE, is not a simple issue since, with the exception of lamotrigine and levetiracetam, prescription of other ASMs is limited by the lack of data both as regard to efficacy and possible teratogenic effects [45].

Chowdhury and Brodie [22] carefully analyzed different treatment schedules in 186 JME patients. They reported earlier remission in male patients, who displayed a complete response to treatment after their first or second ASM; conversely, women achieved remission later in the course of the disease, often requiring a third or further ASM schedule. This effect was attributed to the sex-related differences in the patterns of use of VPA and to the tendency, in women, to switch to other drugs: VPA was present in the 83 % of the men's vs only 60 % of the women's first/second schedules. Other works, too, showed a more frequent use of VPA in men [18,38], but comparable efficacy in men and women [16, 38].

A new work, published too recently for inclusion in our review, confirms these findings: in a cohort of 360 patients with IGE, including a subgroup with JME, significantly fewer women than men were receiving VPA at the last follow-up. The authors found that seizure control was significantly worse among female patients of child-bearing potential compared with men, and that the main factor underlying this difference was the limited use of VPA among women with respect to men [46]. In a previous work, the same authors, studying a group of female IGE patients aged between 13 and 50 years, demonstrated that VPA avoidance or switch might be associated with unsatisfactory seizure control [47].

In addition, differences in treatment adherence can be found between males and females, as disclosed by a study analyzing therapeutic drug monitoring in a JME cohort, in which an inadequate adherence to treatment was found, especially for women, in relation to pregnancy [48]. Although particularly challenging to explore, this issue certainly deserves to be better addressed.

Several studies included in the present review addressed reflex traits (PI, ECS, photosensitivity), which can be present singly or in combination in JME, and were found to have implications for prognosis in some series [11,19,29]. However, few of these studies examined these traits in relation to sex. In the literature, ECS in generalized epilepsies has been reported to show a female predominance [49]. Moreover, it is one of the peculiar features of eyelid myoclonia with absences, a form of epilepsy characterized by an even more marked female prevalence than JME [50]. With regard to JME specifically, Uchida et al., comparing two homogeneous groups of patients with and without ECS, found a predominance of female sex in the group with ECS, and the trait was also related to a worse prognosis in their series [19]. Photosensitivity has a recognized female prevalence [49] and does not seem to be related to a lack of remission in JME [13], even though it was related to a higher risk of relapse after drug discontinuation in one study [51]. Overall, the reasons for the female predominance of these reflex traits involving the visual system are still unknown.

On the other hand, PI was found to be significantly more frequent in male JME patients and related to a worse prognosis [11]. Interestingly, physiological studies exploring the praxis system in animals and humans consistently show a male disadvantage in praxis tasks in comparison with females which seems to derive from a motor planning deficit depending on the dorsolateral prefrontal cortex and supplementary motor area, regions that have shown functional connectivity alterations in JME [52,53]. Thus, sex-related peculiarities in reflex traits may offer intriguing insights into neurobiological and genetic differences between the sexes in humans.

Finally, different studies evaluated EEG features and their possible influence on seizure remission in JME populations. Their discordant results are probably due to the heterogeneity of the study designs and differences in the average number of analyzed EEGs [21].

Our review has certain limitations. The majority of the included studies were retrospective in nature, meaning that a possible recall bias must be taken into consideration. Moreover, considering that many authors evaluating JME prognosis may not have explicitly reported sex analysis results, if not statistically significant, we cannot exclude a reporting bias either.

We acknowledge that RoB evaluation of the included studies was

driven mainly by the purpose of our review, and this, too, may constitute a limitation: some of the studies included were designed to evaluate outcomes other than prognosis or sex differences, and thus their classification as high or moderate RoB may have been overestimated.

The present research is perhaps the first attempt to summarize the existing evidence on sex differences in the long-term outcome of JME. The heterogeneity of the included studies, which were usually performed with other aims, underlines the need for research specifically targeting this issue, with a view to enabling clinicians to provide patients with the most appropriate therapeutic counseling.

5. Conclusion

In conclusion, most studies in JME samples do not highlight sex differences in the long-term prognosis of the disease. However, when analyzing particular JME subpopulations, some sex specificities do emerge, especially with regard to particular reflex traits, such as eye closure sensitivity and praxis induction, which seem to indicate a poorer prognosis. Finally, from the perspective of the current VPA prescription restrictions, knowledge of sex-related differences in prognosis might be helpful in identifying, *a priori*, drug-resistant cases, and thus in ensuring the best available treatment for the single patient.

Further prospective studies exploring JME syndrome in all its complexity are needed to shed more light on the matter.

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Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2021.01.005.

References

[1] Beghi E. The epidemiology of epilepsy. Neuroepidemiology 2020;54:185–91. https://doi.org/10.1159/000503831.
[2] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017. https://doi.org/10.1111/epi.13709.
[3] Kleveland G, Engelsen BA. Juvenile myoclonic epilepsy: clinical characteristics, treatment and prognosis in a Norwegian population of patients. Seizure 1998;7:31–8. https://doi.org/10.1016/s1059-1311(98)90005-x.
[4] Sundqvist A. Juvenile myoclonic epilepsy: events before diagnosis. J Epilepsy 1990;3:189–92. https://doi.org/10.1016/0896-6974(90)90045-Z.
[5] Christensen J, Kjeldsen MJ, Andersen H, Friis ML, Sidenius P. Gender differences in epilepsy. Epilepsia 2005;46:956–60. https://doi.org/10.1111/j.1528-1167.2005.51204.x.
[6] Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. Epilepsy Behav EB 2013;28(Suppl. 1):S15–17. https://doi.org/10.1016/j.yebeh.2012.06.024.
[7] Canevini MP, Mai R, Di Marco C, Bertin C, Minotti L, Pontrelli V, et al. Juvenile myoclonic epilepsy of Janz: clinical observations in 60 patients. Seizure 1992;1:291–8. https://doi.org/10.1016/1059-1311(92)90039-4.
[8] Pal DK, Durner M, Klotz I, Dicker E, Shinnar S, Resor S, et al. Complex inheritance and parent-of-origin effect in juvenile myoclonic epilepsy. Brain Dev 2006;28:92–8. https://doi.org/10.1016/j.braindev.2005.05.009.
[9] Savic I, Engel J. Structural and functional correlates of epileptogenesis - does gender matter? Neurobiol Dis 2014;70:69–73. https://doi.org/10.1016/j.nbd.2014.05.028.
[10] Penry JK, Dean JC, Riela AR. Juvenile myoclonic epilepsy: long-term response to therapy. Epilepsia 1989;30(Suppl. 4):S19–23. https://doi.org/10.1111/j.1528-1157.1989.tb05833.x. discussion S24-27.
[11] Uchida CGP, de Carvalho KC, Guaranha MSB, Guilhoto LMFF, de Araújo Filho GM, Wolf P, et al. Phenotyping juvenile myoclonic epilepsy. Praxis induction as a biomarker of unfavorable prognosis. Seizure 2015;32:62–8. https://doi.org/10.1016/j.seizure.2015.09.011.
[12] Crespel A, Gelisse P, Reed RC, Ferlazzo E, Jerney J, Schmitz B, et al. Management of juvenile myoclonic epilepsy. Epilepsy Behav EB 2013;28(Suppl. 1):S81–86. https://doi.org/10.1016/j.yebeh.2013.01.001.
[13] Stevelink R, Koeleman BPC, Sander JW, Jansen FE, Braun KPJ. Refractory juvenile myoclonic epilepsy: a meta-analysis of prevalence and risk factors. Eur J Neurol 2019;26:856–64. https://doi.org/10.1111/ene.13811.
[14] Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280–6. https://doi.org/10.7326/0003-4819-158-4-201302190-00009.
[15] Sánchez-Zapata P, Zapata-Berruecos JF. Clinical and psychosocial factors associated with seizure control in patients with juvenile myoclonic epilepsy. Rev Neurol 2019;69:453–60. https://doi.org/10.33588/rn.6911.2019305.
[16] Gürer R, Aydın Ş, Özkara Ç. Outcomes of low-dose valproic acid treatment in patients with juvenile myoclonic epilepsy. Seizure 2019;70:43–8. https://doi.org/10.1016/j.seizure.2019.06.021.
[17] Syvertsen M, Fløgstad I, Enger U, Landmark CJ, Koht J. Antiepileptic drug withdrawal in juvenile myoclonic epilepsy. Acta Neurol Scand 2019;139:192–8. https://doi.org/10.1111/ane.13042.
[18] Zhang Y, Chen J, Ren J, Liu W, Yang T, Zhou D. Clinical features and treatment outcomes of Juvenile myoclonic epilepsy patients. Epilepsia Open 2019;4:302–8. https://doi.org/10.1002/epi4.12321.
[19] Uchida CGP, de Carvalho KC, Guaranha MSB, Guilhoto LMFF, de Araújo Filho GM, Yacubian EMT. Prognosis of Juvenile myoclonic epilepsy with eye-closure sensitivity. Seizure 2018;62:17–25. https://doi.org/10.1016/j.seizure.2018.09.006.
[20] Cação G, Parra J, Mannan S, Sisodiya SM, Sander JW. Juvenile myoclonic epilepsy refractory to treatment in a tertiary referral center. Epilepsy Behav EB 2018;82:81–6. https://doi.org/10.1016/j.yebeh.2018.03.002.
[21] Arntsen V, Sand T, Syvertsen MR, Brodtkorb E. Prolonged epileptiform EEG runs are associated with persistent seizures in juvenile myoclonic epilepsy. Epilepsy Res 2017;134:26–32. https://doi.org/10.1016/j.eplepsyres.2017.05.003.
[22] Chowdhury A, Brodie MJ. Pharmacological outcomes in juvenile myoclonic epilepsy: support for sodium valproate. Epilepsy Res 2016;119:62–6. https://doi.org/10.1016/j.eplepsyres.2015.11.012.
[23] Asadi-Pooya AA, Hashemzehi Z, Emami M. Predictors of seizure control in patients with juvenile myoclonic epilepsy (JME). Seizure 2014;23:889–91. https://doi.org/10.1016/j.seizure.2014.08.004.
[24] Jović NJ, Kosać A, Babić MD. Terminal remission is possible in some patients with juvenile myoclonic epilepsy without therapy. Med Pregl 2014;67:372–8. https://doi.org/10.2298/mpns1412372j.
[25] Syvertsen MR, Thuve S, Stordrange BS, Brodtkorb E. Clinical heterogeneity of juvenile myoclonic epilepsy: follow-up after an interval of more than 20 years. Seizure 2014;23:344–8. https://doi.org/10.1016/j.seizure.2014.01.012.
[26] Tekin Güveli B, Baykan B, Dörtcan N, Bebek N, Gürses C, Gökyiğit A. Eye closure sensitivity in juvenile myoclonic epilepsy and its effect on prognosis. Seizure 2013;22:867–71. https://doi.org/10.1016/j.seizure.2013.07.008.
[27] Senf P, Schmitz B, Holtkamp M, Janz D. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. Neurology 2013;81:2128–33. https://doi.org/10.1212/01.wnl.0000437303.36064.f8.

[28] Pavlović M, Jović N, Pekmezović T. Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. Seizure 2011;20:520–5. https://doi.org/10.1016/j.seizure.2011.03.007.
[29] Guaranha MSB, Filho GMde A, Lin K, Guilhoto LMFF, Caboclo LOSF, Yacubian EMT. Prognosis of juvenile myoclonic epilepsy is related to endophenotypes. Seizure 2011;20:42–8. https://doi.org/10.1016/j.seizure.2010.10.004.
[30] Demirkaya N, Vanli Yavuz EN, Altindağ E, Baykan B. Clinical and EEG analysis of patients with idiopathic generalized epilepsy and photosensitivity. J Neurol Sci 2009;26:26–33.
[31] Simard-Tremblay E, Shevell M. A profile of adolescent-onset epilepsy. J Child Neurol 2009;24:1243–9. https://doi.org/10.1177/0883073809334381.
[32] Baykan B, Altindag EA, Bebek N, Ozturk AY, Aslantas B, Gurses C, et al. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. Neurology 2008;70:2123–9. https://doi.org/10.1212/01.wnl.0000313148.34629.1d.
[33] Mohanraj R, Brodie MJ. Outcomes of newly diagnosed idiopathic generalized epilepsy syndromes in a non-pediatric setting. Acta Neurol Scand 2007;115:204–8. https://doi.org/10.1111/j.1600-0404.2006.00791.x.
[34] Radhakrishnan K, St Louis EK, Johnson JA, McClelland RL, Westmoreland BF, Klass DW. Pattern-sensitive epilepsy: electroclinical characteristics, natural history, and delineation of the epileptic syndrome. Epilepsia 2005;46:48–58. https://doi.org/10.1111/j.0013-9580.2005.26604.x.
[35] Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. J Neurol Neurosurg Psychiatry 2001;70:240–3. https://doi.org/10.1136/jnnp.70.2.240.
[36] Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. Epilepsia 1994;35:285–96. https://doi.org/10.1111/j.1528-1157.1994.tb02432.x.
[37] Matsuoka H. The seizure prognosis of juvenile myoclonic epilepsy. Jpn J Psychiatry Neurol 1992;46:293–6. https://doi.org/10.1111/j.1440-1819.1992.tb00861.x.
[38] Johannessen Landmark C, Fløgstad I, Syvertsen M, Baftiu A, Enger U, Koht J, et al. Treatment and challenges with antiepileptic drugs in patients with juvenile myoclonic epilepsy. Epilepsy Behav EB 2019;98:110–6. https://doi.org/10.1016/j.yebeh.2019.05.021.
[39] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classi- fication of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99. n.d.
[40] Baykan B, Martínez-Juárez IE, Altindag EA, Camfield CS, Camfield PR. Lifetime prognosis of juvenile myoclonic epilepsy. Epilepsy Behav EB 2013;28(Suppl. 1):S18–24. https://doi.org/10.1016/j.yebeh.2012.06.036.
[41] Janz D. Juvenile myoclonic epilepsy. Epilepsy with impulsive petit mal. Cleve Clin J Med 1989;56(Suppl. Pt 1):S23–33. discussion S40-42.
[42] Anonymous. New measures to avoid valproate exposure in pregnancy endorsed. Eur Med Agency; 2018 (Accessed 5 September 2020), https://www.ema.europa.eu/en/news/new-measures-avoid-valproate-exposure-pregnancy-endorsed.
[43] Tabrizi N, Zarvani A, Rezaei P, Cheraghmakani H, Alizadeh-Navaei R. Levetiracetam in genetic generalized epilepsy: a prospective unblinded active-controlled trial. Epilepsy Res 2019;157:106214. https://doi.org/10.1016/j.eplepsyres.2019.106214.
[44] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology 2015;85:866–72. https://doi.org/10.1212/WNL.0000000000001772.
[45] Mostacci B, Ranzato F, Giuliano L, Neve AL, Aguglia U, Bilo L, et al. Alternatives to valproate in girls and women of childbearing potential with Idiopathic Generalized Epilepsies: state of the art and guidance for the clinician proposed by the Epilepsy and Gender Commission of the Italian League Against Epilepsy (LICE). Seizure - Eur J Epilepsy 2020. https://doi.org/10.1016/j.seizure.2020.12.005.
[46] Cerulli Irelli E, Cocchi E, Morano A, Casciato S, Fanella M, Albini M, et al. Valproate impact and sex-dependent seizure remission in patients with idiopathic generalized epilepsy. J Neurol Sci 2020;415:116940. https://doi.org/10.1016/j.jns.2020.116940.
[47] Cerulli Irelli E, Morano A, Cocchi E, Casciato S, Fanella M, Albini M, et al. Doing without valproate in women of childbearing potential with idiopathic generalized epilepsy: implications on seizure outcome. Epilepsia 2020;61:107–14. https://doi.org/10.1111/epi.16407.
[48] Johannessen Landmark C, Fløgstad I, Baftiu A, Syvertsen M, Enger U, Koht J, et al. Long-term follow-up with therapeutic drug monitoring of antiepileptic drugs in patients with juvenile myoclonic epilepsy. Epilepsy Res 2019;155:106148. https://doi.org/10.1016/j.eplepsyres.2019.05.016.
[49] Martins da Silva A, Leal B. Photosensitivity and epilepsy: current concepts and perspectives-A narrative review. Seizure 2017;50:209–18. https://doi.org/10.1016/j.seizure.2017.04.001.
[50] Giuliano L, Fatuzzo D, Mainieri G, Maira G, Elia M, Ferlazzo E, et al. Eyelid myoclonia with absences: electroclinical features and prognostic factors. Epilepsia 2019;60:1104–13. https://doi.org/10.1111/epi.15157.
[51] Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, et al. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25-63 years of follow-up. Epilepsia 2012;53:1379–86. https://doi.org/10.1111/j.1528-1167.2012.03526.x.
[52] Vollmar C, O'Muircheartaigh J, Barker GJ, Symms MR, Thompson P, Kumari V, et al. Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study. Brain J Neurol 2011;134:1710–9. https://doi.org/10.1093/brain/awr098.
[53] Cohen NR, Pomplun M, Gold BJ, Sekuler R. Sex differences in the acquisition of complex skilled movements. Exp Brain Res 2010;205:183–93. https://doi.org/10.1007/s00221-010-2351-y.