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Review Article

The Delayed Diagnosis of Juvenile Myoclonic Epilepsy in Young Adults: A Scoping Review

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Abstract

Introduction: The most prevalent idiopathic generalized epilepsies of adolescence and early adulthood is juvenile myoclonic epilepsy (JME). Its diagnosis is usually missed, wrongly labeled, and frequently delayed worldwide. This scoping review focused on the factors that contribute to JME diagnosis delays and how to avoid them.

Methodology: The preferred reporting items for systematic reviews and meta-analysis protocols for comparative published articles were used. To determine the factors that cause the delay of diagnosis of JME, a search in PubMed and ScienceDirect (Summon) using keywords "JME" and "Janz epilepsy" revealed a sum of 13410 articles. However, when including the keywords; 'delayed diagnosis', 'human',' English language', 'young adults' and 'free full text'; and excluded 'duplicated and unrelated articles we remained with 15 articles. The participants were young adult patients.

Results: Out of the 15 articles two have reported a delay in the diagnosis of JME by14 years, while the rest varied from 1 to 11 years. With the mean age of delay being 20 ±10 years. One of the various reasons contributing to this delay is failure to elicit a myoclonic jerk history due to lack of familiarity with the syndrome which accounted for 93.3%, followed by misleading or misinterpretation of EEG 86.6%, normal EEG 80%, presenting initial seizure with GTC 66.67% and patients fail to mention their own myoclonic jerks 60%.

Conclusion: Despite well-defined diagnostic criteria and growing public knowledge of JME, misdiagnosis remains an issue that causes the delay by several years.

***Keywords:** Delayed diagnosis; Juvenile myoclonic epilepsy (JME); Young adults; Epilepsy syndrome.*

Introduction

The most prevalent idiopathic generalized epilepsies of adolescence and early adulthood is juvenile myoclonic epilepsy (JME). Myoclonic jerks are the hallmark of this condition, which can manifest as focal, generalized tonic-clonic (GTCS), or absence seizures. Because of this presentation and other factors, JME is frequently missed, mislabeled, or delayed in diagnosis around the world. Seizures tend to occur pretty shortly after waking up and are often triggered by sleep deprivation.

In 1867, Herpin was the first to describe JME; however, in 1957, Mathes and Janz described the condition's clinical and EEG aspects, giving it the name Janz syndrome.

Previous studies have found a 14.5-year delay in diagnosing JME [1, 3]. Patients frequently came to seek medical attention only after a GTCS. Diagnostic delay is a common medical error, it occurs when the doctor takes a longer time interval between the appearance of symptoms and the confirmation of a disease's diagnosis. Which can lead to more complications and even can result in death.

Diagnosis of JME is typically based on patient history. Because almost all tests including physical examination, MRI, and CT scans will be normal. Also, it depends on the doctor's familiarity with the myoclonic jerks, which are the defining feature of the syndrome. Additionally, the generalized 3.5-6 Hz single, bifid, and polyspikes slow-wave complexes on a normal brain background activity are prominent and cardinal EEG features of JME syndrome that support the diagnosis [2].

Aim

The goal of this study is to review previous JME articles to figure out what's causing delay in diagnosis.

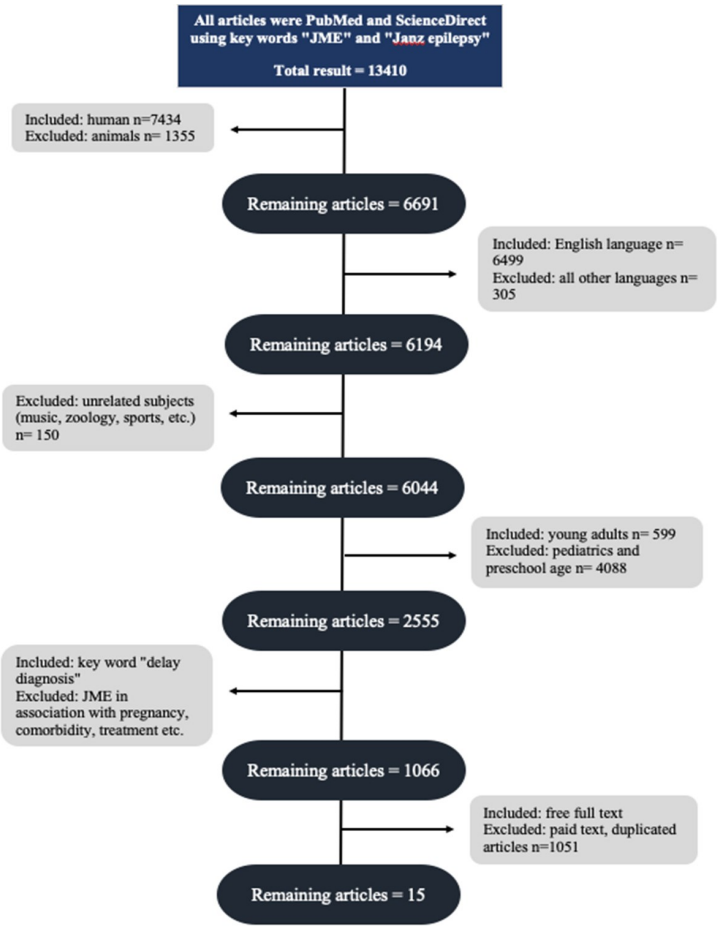
Objective

To review the literature and determine the factors that cause a delay in JME diagnosis.

To review previous studies in JME and find the factors that help avoid its delayed diagnosis

Protocol

The preferred reporting items for systematic reviews and meta-analysis protocols for comparative published articles were used. 13410 articles were found in PubMed and ScienceDirect (Summon) using key words "JME" and "janz epilepsy". However, our inclusion criteria are articles that include key word 'delay diagnosis', 'human',' English language', 'young adults', 'free full text. On the other hand, the exclusion criteria are 'unrelated subjects', 'duplicated articles' and that not meeting inclusion criteria. According to these criteria the remaining are 15 articles.



Methods and Results

Panayiotopoulos et al Carried out their research between 1983 and 1988 on seventy patients, chosen based on clinical and EEG criteria that have been well-defined. All JME patients who had not been diagnosed at an epilepsy center were assessed. The medical records, as well as a reevaluation of the patient's history and EEG, were utilized to investigate the reasons that led to the accurate diagnosis being missed. The mean duration of delay time until the correct diagnosis was 8.3 ± 5.5 years and 17.7± 10.4 months following an initial assessment at an epilepsy clinic.

The delay in diagnosis was caused by the following factors: Myoclonic jerks were absent in 19 of the 22 cases. Fourteen patients were not particularly questioned about myoclonic jerks; two patients' myoclonic jerks were not disclosed despite specific questioning; and Four patients with unilateral jerks were wrongly diagnosed as having partial motor seizures. Moreover, the EEG revealed typical generalized abnormalities for 14 out of 22 patients. Focal EEG abnormalities paired with patient complaints of mostly unilateral jerks misled the diagnosis to partial seizures with secondary GTCS in three patients. Normal or nonspecific EEG abnormalities were found in eight cases [3].

Grunewald et al, performed their study that included 15 cases of JME patients out of 180 consecutive referrals at St Thomas' Hospital epilepsy clinic, the study was conducted between the year 1989 and 1990, all patients had GTCS and myoclonic jerks. While only Six of all the patients (40%) had clinical absences which started at the mean age of 9.5 years, and GTCS were at 16.1 years and myoclonic jerks started at 14.3 years. They discovered that the average age of JME diagnosis was 27.7 years (range 13-41) and that there was a 14.5-year delay in diagnosis (range 1-33 years) [1, 3].

Sharpe and Buchanan performed their study on Thirty- six patients with JME the mean age was 30 ± 10.9 years attending an epilepsy clinic at a tertiary referral hospital to study delay diagnosis in patients with (JME). They look over their medical records and interviews all patient. The mean age at which epilepsy began was 14.1± 3.3 years. At the time of initial presentation, 20 patients had only GTCS, 11 had absences as well as tonic-clonic seizures, four patients had just absences, and one patient had only early-morning myoclonus. The mean duration of the delay in the diagnosis was 9.7 ± 10.3 years. Seizure-provoking factors are very common in juvenile myoclonic epilepsy. At least one provoking factor was noted by all cases. Sleep deprivation 83% of patients, stress 47%, alcohol 47%, Myoclonic jerks were reported by all patients; they were symmetrical in 86% of cases, affecting just the upper limbs in 47 % of cases, the entire body in 39 % of cases, and the lower limbs in only 14% of cases. Thirty-two patients experienced myoclonus shortly after waking up, and six patients had myoclonic jerks after washing their faces in the morning [4].

Kleveland & Engelsen had selected 43 patients that were presented with juvenile myoclonic epilepsy and have attended Haukeland University Hospital's neurological department. The patients were set to complete a standard questionnaire on their condition such as: epilepsy onset, kinds and frequency of seizures, medical history, therapy, seizure management. As well as the presence of myoclonic jerk. Patients mean age was 29 ±9 year, and seizure onset had a mean age of 15 ± 2.8 years. As for the age in which a diagnosis was made, 16 ± 4.1 years were reported. The first seizure type reported by the patients was GTCs, while nine have reported myoclonic seizure, and only one reported absence seizures as their first seizure type. One patient had a combination of myoclonic seizure and absence seizures, and ten have had GTCs preceding absence seizures as their initial seizure type [5].

Gunatilake & Seneviratne, Follow-up study over a period of 3 years. This study included forty patients. At the first visit, the patients' ages ranged from 12 to 58 (mean 25.9). The disease first showed up in people between the ages of 10 and 37 (mean 16.4). All the patients had myoclonic jerks, although only six of them told us about them. Myoclonic jerks were observed in 23 patients when they awoke in the morning. In these patients, sleep deprivation was the most common precipitating factor. Stress arithmetic, alcohol, and menstruation were among the other triggers. In 14 patients, the EEG was normal; in 17 patients, it was abnormal, and seven of them had polyspike and slow wave paroxysms. In nine patients, the EEG was unavailable. The average time between diagnosis and treatment was 11 years. Patients who were not complaining of myoclonic jerks and typically interpret the jerks as falls, shivers, and dropping of objects, and the significance of these symptoms can easily be overlooked in 34 patients, EEG changes that were not typical in 10 patients, and the doctor unaware of the syndrome in at least 28 of the patients who had both myoclonic jerks and tonic–clonic seizures, up to 25% of JME patients have been reported to have absence seizures, but none of our patients have reported having them [6].

Dhanuka et al Conducted their study on 24 JME patients, who attended to Dayanando Medical College in India, during a period extended from January 1998 to July 1999. The mean age at which symptoms first appeared was 12.17 ± 3.513 years, and the average period at diagnosis was 15.40 ± 3.247 years. Almost all patients were referred from another hospital. Unfortunately, none of the referred patients were diagnosed with JME earlier because of that, there was a diagnostic delay of 3.5 years. Initial routine EEG was normal in 27% of cases, appeared typical changes in 54% and misleading or unspecific in 20%. Sleep EEG was abnormal in all patients (100%) with GSW, GPSW and slow wave discharges. They consider that the sleep EEG is a more specific and sensitive tool for diagnosing JME, while the routine awake EEG can miss or be misleading. [7].

A study performed by Mehndiratta & Aggarwal, included 103 patients diagnosed with JME, who were taken from a super specialty university hospital in India. The average age of patients at disease onset was 14.01 ± 3.14 years, while the mean age of diagnosis was 21.91 ± 7.12 years. They discovered that the initial EEG of four (4.8%) patients was normal, but a repeated EEG showed spike and wave discharges. However, the correct diagnosis was established after an average of 5.26 ± 4.61 years from the onset of the disease [8].

Betting & Cendes performed their study on Eighty (n=80) patients diagnosed with JME were studied to determine the role of EEG in idiopathic generalized epilepsy patients and how it can aid in diagnosis and treatment, they included all patients in their epilepsy clinics who had generalized seizures that were compatible with IGE in between 2000 and 2005. They reinterviewed patients and at least one person who witnessed typical seizures. All EEG tracings and medical records were reevaluated. The patients' average age at the time of assessment was 30.3 years old, while the average age when the seizures started was 12.2 years old. In 35 of the cases, the initial EEG exams revealed no abnormalities, atypical abnormalities in 16 cases, and typical abnormalities in 29. The first EEG was done on average 9.9±8.8 years after the first seizure, with a mean delay of 14.1±10 years [9].

Sousa et al. studied 41 individuals averaging age was from 16 to 50 years old. Before being treated at the Escola Paulista de Medicina, these patients had not been diagnosed with JME. In an average of 8.2 years, the diagnosis was made (15 days to 34 yr). Omission, asymmetry of myoclonic, normal first EEGs, and the presence of focal abnormalities in the EEGs were all recognized as reasons in the delayed diagnosis. When sleep-deprived EEGs were electrographically described, 32 individuals displayed epileptiform activity, while nine recordings were classified normal. GPSW was present, and an irregular generalized spike occurred at (4-6Hz/wave) [10].

Shahnaz1 et al. studied 60 JME patients. The patients' age range was 20.354.94. Myoclonic jerks (MJ) were found in all individuals, as well as GTCS, absence seizures, and myoclonic seizures in a few. Sleep deprivation, weariness, stress, menstruation, television viewing, and video game playing were all present in the majority of the patients. There was no specific triggering factor in six (10%) of the patients. Only 6 individuals had JME, 6 had seizure disorder, 18 had epilepsy, 22 had GTCS, and 8 had partial seizures, according to the referring physicians' diagnoses. 5.22 years was the average time it took to get a diagnosis (ranged from 4-10 years). In terms of EEG findings, The EEGs of 18 of the patients were normal, whereas the EEGs of the other 18 patients were abnormal (42 patients). Patients with abnormal EEG had generalized (4-6-Hz) polyspike and wave activity, generalized single spike/ sharp waves, and 3-Hz SW activity in addition to the PSW pattern [11].

Dilek Atakli et al performed his study on 76 JME patients (27 females and 49 males). JME was diagnosed in all of the patients based on clinical and EEG results. JME was discovered in 76 (5.8%) of 1300 epilepsy patients. Myoclonic jerks (MJ) were discovered in all 76 individuals. Thirty-one people also had absence seizures (AS) while 63 people suffered GTCS. Only five of our patients had MJ, 40 had MJ and GTCS, eight had MJ and AS. and 23 had both AS and MJ. precipitating causes were discovered in 65 cases. The most common causes were sleep deprivation, photic stimulation, stress, fatigue, and menstruation. The neurological and mental examinations of all patients were normal. At the initial evaluation, 40 of the 76 patients were misdiagnosed. At the time of the accurate diagnosis, the average age was 22.5 13.5 years (12- 38 years). A definitive diagnosis takes an average of 5.9 years to get. (from 6 months to 14 years) [12].

Dilek Atakli et al. did another study in 2016, that included 200 JME patients aged 12 to 55 were assessed at epilepsy outpatient clinics in Turkey to determine misdiagnosis in JME. All of the patients' medical records were evaluated. Age of seizure onset 15.26 ± 4.1 (9–35). Participants were separated into two groups: those who received a correct initial diagnosis and incorrect initial diagnosis. 151 patients had their initial medical intervention correctly diagnosed, while the diagnosis was delayed in 45 patients due to late admission to the hospital and ignorance of myoclonia as the first presenting seizure. 49 patients, on the other hand, were given the wrong diagnosis. The average time it took to get the accurate diagnosis was 3.14.1 years. The first seizure in the misdiagnosed group that caused the patients to seek medical help was a GTCS, and their EEG showed generalized spike wave (GSW) and polyspike-wave (GPSW) discharges. The majority of correctly diagnosed patients, on the other hand, were admitted to the hospital with myoclonia and focal EEG discharges [13].

Abdalla et al, done their study on 3523 Sudanese patients, they were evaluated in El-Magzoub Neurosciences center, between March 2003 and May 2012. Patients with abnormal brain imaging, a history of severe head trauma, or an apparent neurological disability were excluded from the study, they were left with 2063 patients at the end. They found that the average age of Sudanese patients diagnosed with JME was 19.55 ±8.98 years, with a diagnostic delay of 4.35 years [2].

A study performed by Murthy et al, cases of JME patients who had visited Nizam's Institute of Medical Science's epilepsy clinic located in South India were included in their study. The study consisted of 131 cases of JME that were reported at the clinic up to June of 1994. Patients were investigated prospectively using a standard technique, which included documenting seizures and triggering factors. The patients had a mean age of onset which was 13.37 ±4.93 years, and their diagnosis was made at a mean age of 19.53 ±7.85 years. Early onset absences were present in 16% of patients (21 pt). The onset of the diagnosis was delayed in 4.6 % of patients (6 pt). They also discovered that absences in all of the patients preceded other forms of seizures, they also stated that myoclonic jerks were mainly unilateral in 16.8% of them (22 pt). As for the initial EEG, it showed generalized spikes, paroxysms of spike slow wave in 81% of all patients records. They stated that there was a delay in the diagnosis of 36 patients [14].

Another study was established by Murthy in the year 1999 where he conducted his study on the same 131 patients. The mean age when the first symptoms appeared was 13.37 +4.83 years. They found out there was a great delay of about 6.8 + 6.3 years in the diagnosis. The study revealed the possible factors for delaying the diagnosis of JME are poor physicians' awareness of JME and lack of familiarity with myoclonic jerks, this was the reason for the delay in diagnosis of JME in 82.4%. EEG's misinterpretation was also likely the factor delaying diagnosis in 18.6% of patients [15].

Table 1: Data extraction.

Article No.	Authors	Year of publication	Study population	Mean age of the onset (yr, range)	Mean age of the diagnosis (yr, range)	Duration of delay diagnosis (yr, range)
1	Panayiotopoulos et al	1991	70	-	-	8.3 ±5.5
2	Grunewald et al	1992	15	-	27.7	14.5
3	Sharpe and Buchanan	1995	36	14.1 ±3.3	30 ±10.9	9.7 ±10.3
4	Murthy et al	1998	131	13.37 ±4.93	19.53 ±7.85	6.16 ±2.92
5	Kleveland & Engelsen	1998	43	15 ±2.8	16 ±4.1	1 ±1.3
6	Dilek Atakli et al	1998	76	12.5 ±2.12	-	5.9
7	Murthy	1999	131	13.37 +4.83	20.17 +10.86	6.8 +6.3
8	Gunatilake & Senevirat-ne	2000	40	16.4	-	11
9	Dhanuka et al	2001	24	12.17 ±3.513	15.40 ±3.247	3.5
10	Mehndiratta & Aggarwal	2002	103	14.01 ±3.14	21.91 ±7.12	5.26 ±4.61
11	Betting & Cendes	2006	80	12.2 ±3.8	30.3 ±9.2	14.1 ±10
12	Sousa et al.	2006	41	-	10.8	8.2
13	Shahnaz1 et al.	2014	60	13.7 ±2.12	-	5.2
14	Atakli et al	2016	200	15.26 ±4.1	-	3.1 ±4.1
15	Abdalla et al	2017	2063	10 ±4.81	19.55 ±8.98	4.35

Discussion

Despite the fact that JME is a well-known epileptic disorder that can be easily diagnosed thorough clinical history, it is still diagnosed incorrectly and/or late for a variety of reasons. The majority of articles reported myoclonic jerks as the first seizures type which are a hallmark of JME and are frequently overlooked or misdiagnosed as epileptic seizures by patients. Abdalla et al and Sharp et al reported that all patients experienced myoclonic jerks, with the upper limb bore bearing the highest percentage of jerks, followed by jerks over their entire body and lower limb jerks [2, 4].

This could be one of the reasons why JME remains underdiagnosed. 53.3% of the studies reported myoclonic jerks as the initial symptom, whereas 33.3% recorded GTCs before Myoclonic jerks, and only one publication indicated absences as the first manifestation, accounting for 6.6%. The diagnosis may be delayed in patients whose GTC and absence seizures occur before myoclonic jerks.

In JME triggering factors are common, highlighting the significance of lifestyle issues in seizure control. JME is a circadian -related disorder, which implies that its symptoms are affected by the sleep-wake cycle. The amount of discharges increased as the transition from as the transition from sleep to wakefulness occurred, while the number of discharges decreased when the shift to slow-wave sleep occurred [8]. Sharpe and Buchanan found that 16% of patients had a myoclonic jerk after washing their faces in the morning, indicating that eye closure after waking up can trigger myoclonus. Sleep deprivation is the most common seizure-inducing cause, which is mentioned in all of the articles [5, 11]. Also, some articles reported that seizures occurred after awakening in some patients [13] [6]. Photic stimulation and light were present in most articles [9] [14], alcohol supported by some articles [5]. Some articles have also mentioned other seizure precipitating factors like stress, fasting, puberty, and fatigue.

The most common test used to diagnose JME is the EEG, while MRI and CT scan usually show normal results; this was supported by a study in which 36 patients had brain MRI and CT scans when indicated, and all the results were normal [8]. The EEG is crucial for evaluating patients with JME. The most common feature is a GSW and/or GPSW discharges with a frequency of 3.5 to 6 Hz, as seen in the majority of the articles. The most critical characteristic in JME, according to Betting & Cendes and Atakli et al research, is normal background, that is particularly significant for differential diagnosis with progressive myoclonic epilepsy that begins in adolescence [9,13]. The most prevalent provocative procedures used while recording EEG were hyperventilation and photic stimulation.

In our review, the majority of articles found that the most common factors causing delayed diagnosis of JME are unfamiliarity with the syndrome among the physicians and failure to elicit a history of myoclonic jerk, which accounts for 93.3% of all articles. Abdalla et al and Panayiotopoulos et al reported that some physicians may misdiagnose unilateral myoclonic jerks as partial seizures. This diagnosis can be supported by the finding of focal EEG abnormalities. They have been accused by several investigators as the primary cause of missed and delayed diagnoses, as it might be ignored. The second most common cause was misleading or misinterpretation of EEG. Focal anomalies that could lead to a diagnosis of partial epilepsy with secondary generalization were seen in 86.6% of the articles. Also, 80% of the articles reported that the initial EEG might be normal. Patients tend to seek help when GTCS are present thus it is one of the most frequent causes contributing to misdiagnosis when being presented as the first seizure type, which account 66.67% of all articles.

The patient's failure to acknowledge or deny the occurrence of myoclonic jerks is one of the variables leading to the high rate of misdiagnosis which were reported by 60% of all articles. [6] claims that although up to 25% of JME patients have been reported to suffer absence seizures, none of the patients admitted to having them. This could be for a variety of reasons, including the fact that patients with myoclonic jerks and seizures are more prone to overlook or forget these little lapses; absences in JME are also reported to be so slight that they might get mistaken for other types of seizures like complex partial seizure. Also, patients have reported myoclonic jerks as shivers, dropping things and falls, early morning clumsiness, and nervousness or an unrelated symptom.

Due to its particular prognosis and treatment, failure to get the right diagnoses of JME not only increases patient morbidity, but it also confounds the analysis of research done on insufficiently classified epileptic populations. Most articles have reported that in order to solve these issues:

1. Each patient presented with a history of myoclonic jerks, shaking, and morning clumsiness or anxiety should be examined. Furthermore, if a patient with GTCS is observed, JME should be recalled, and appropriate time spent on a complete clinical questionnaire should be done, as most patients with JME will have GTCS.

2. A syndromic categorization of epilepsy should be noted for each patient and revisited at a later date. especially if their fits are uncontrollable.; During the follow-up, the physician should be interested and persistent While posing inquiries to the patient.

3. Even if focal abnormalities are present, the diagnosis of partial seizures should be reviewed if the EEG reveals generalized spikes or spike and slow-wave discharges. [1, 3] The following passages from a patient's diary were discovered in hospital records dated fifteen years before diagnosis, according to their study: "Lots of blanks and jerks; then I had a grand mal ... I usually have fits when rushing after getting up; usually does not happen later in the day". Because of focal abnormalities on the EEG and a feeling of terror during her absence seizures, she was diagnosed with complex partial seizures.

Despite growing awareness, the current study finds that a quarter of JME patients were not adequately diagnosed on their first visit, despite being examined [13]. JME diagnosis requires a thorough understanding of the illness, as well as obtaining a history of and appropriately interpreting myoclonic seizures, both of which can be improved with better medical awareness. EEG should be used in conjunction with other diagnostic techniques.

Table 2: Main cause of the delay in the diagnosis.

Article No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Lack of familiarity with the JME and/or failure to elicit a history of myoclonic jerking	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93.3%
mislead or misinterpretation of EEG	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	86.6%
Normal EEG	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	80%
Presenting initial seizure with GTC	-	+	-	+	-	+	+	-	-	+	+	+	+	+	+	66.67%
Patients fail to mention their own myoclonic jerks	-	+	-	-	+	-	+	+	-	-	+	+	+	+	+	60%

Limitations

In this scoping review, we sought to clarify the delay in the diagnosis of JME and analyze possible causes that may provide additional knowledge about the syndrome to prevent such delay in the diagnosis. Several limitations of this study exist. First, there is limited data due to several reasons one being that there are only a few studies that focus on the delay, only English language articles have been reviewed which may result in missing potentially good-quality recourses available in other languages. The second limitation we came across was access to literature as we only were able to collect full free text thus, limited our review to access a larger range of literature.

Conclusion

We have demonstrated that JME is a well-known idiopathic generalized epilepsy syndrome. Despite well-defined diagnostic criteria and growing public knowledge of JME, misdiagnosis remains an issue that causes the delay by several years due to various reasons including Variability in EEG features, inadequate understanding of the disease, insufficient history taking of myoclonic jerk. MJs are the cardinal presenting symptoms that occurs predominantly on waking and is usually exacerbated by sleep deprivation. Typical EEG features a normal background with GSW or GPSW occurring at 4-6 Hz. JME has a significant and precise impact on prognosis and therapeutic decisions when diagnosed correctly. If JME is not detected, it can lead to uncontrollable seizures, status epilepticus, irreparable brain damage, and even death in advanced cases. Remains a clear need for further research to provide sufficient data, we suggest future research to evaluate JME patients through long-term monitoring, as the first routine EEG shows normal values in most patients. Also, the discharge tends to appear during the transition from sleep to an awake state.

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