Antiseizure Medications Withdrawal Seizures in Patients with Juvenile Myoclonic Epilepsy

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ABSTRACT

Background: Patients with juvenile myoclonic epilepsy (JME) are especially prone to having antiseizure medications (ASMs) withdrawal seizures (WS).

Objectives: To clarify whether WS in JME patients are caused by a high tendency of non-adherence from seizure-free patients or by a constitutive increased sensitivity to drug withdrawal.

Methods: Epilepsy patients followed in a tertiary epilepsy clinic between 2010 and 2013 were included in the study. WS prevalence was compared between drug-responsive and drug-resistant JME patients and patients with other types of epilepsy.

Results: The study included 23 JME patients (16 drug-responsive and 7 drug-resistant) and 138 patients with other epilepsies (74 drug-responsive and 64 drug-resistant). JME patients were younger and included more women than non-JME patients. Significantly more WS were seen in JME than in non-JME patients (P = 0.01) and in the drug-resistant fraction of JME patients in comparison to drug-resistant non-JME patients (P = 0.02). On logistic regression, the type of epilepsy, but not the patient’s sex, was found to significantly predict WS. No significant difference was found in the prevalence of WS between drug-responsive and drug-resistant JME patients. The main ASM discontinued in JME was valproic acid (VPA), especially in women.

Conclusion: Our findings suggest a higher sensitivity of JME patients to withdrawal of medications. It is important to educate JME patients about treatment adherence and to explain to their physicians how to carefully reduce or replace ASMs to mitigate the morbidity and mortality related to ASM withdrawal.

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KEY WORDS: antiseizure medication (ASM), drug-resistant epilepsy, valproic acid, juvenile myoclonic epilepsy (JME), withdrawal seizures

Juvenile myoclonic epilepsy (JME) is a common type of primary generalized epilepsy. Most patients with JME respond well to antiseizure medications (ASMs), and 8-25% of patients with JME continue to be seizure free years after termination of the drug treatment [1-6]. However, patients with JME are especially prone to seizure relapse after cessation of drug therapy [2]. For example, Canavini et al. [7] reported withdrawal seizures (WS) during the first year following drug cessation in all eight JME patients who stopped ASMs. One explanation for the high prevalence of WS in JME is that this type of epilepsy is usually drug responsive and the patients or physicians tend to stop the medications after long seizure-free periods [5]. However, it is not clear whether the relatively high risk for WS is limited only to the drug-responsive JME patients. If it is, WS prevalence would be similar in drug-resistant JME patients and in drug-resistant patients with other epilepsy types.

The aim of this study was to determine whether both drug-responsive and drug-resistant JME patients have more WS than patients with other types of epilepsy. Thus, we evaluated the prevalence of WS in a group of drug-resistant and drug-responsive patients with JME as well as with other epilepsy syndromes.

PATIENTS AND METHODS

The study was approved by the institutional review board of the Hadassah Medical Organization and Faculty of Medicine, Jerusalem, Israel, and conducted in accordance with their guidelines (protocol number HMO-0293-11). The approval included a waiver of informed consent since the presented data do not reveal identifying information of the individual patients. The clinical data were retrospectively collected from the patients, their family members, and old medical files during the first clinical visit and prospectively collected during the following visits. The study included patients treated at the Epilepsy Outpatient Clinic at Hadassah Medical Center between August 2010 and February 2013. Patients without a clear diagnosis of epilepsy or with non-epileptic seizures were excluded. We also excluded patients with progressive neurological conditions causing epilepsy, such as malignant tumors. The data were gathered from the hospital’s electronic recordings.
Epilepsy was classified according to the ILAE classification of seizures and epilepsy [8]. In general, drug-resistant epilepsy was defined as failure of adequate trials of at least two tolerated and appropriately chosen and used ASM schedules to achieve sustained seizure freedom [9]. However, patients with JME were considered drug-responsive if they had complete control of tonic-clonic and absence seizures, even if they still experienced occasional non-detrimental myoclonic jerks.

WS were defined as seizures that occurred following discontinuation or dose reduction of an ASM, both if the ASM change was performed per physician’s recommendation or as non-adherence of the patient to the treatment. In cases of patients with more than one event of WS we referred only to the first event.

A t-test was used to compare continuous variables between the JME and non-JME epilepsy patients. Chi-square test was used to compare proportions and logistic regression to test the effect of JME as well as patient sex on the risk of having WS. *P* value < 0.05 was considered significant.

**RESULTS**

**GENERAL CHARACTERISTICS OF THE PATIENTS IN THE STUDY**

Data from 161 epilepsy patients, 23 with JME and 138 with non-JME epilepsy, were included in the study [Table 1]. Patients with JME were younger (mean age 33 years vs. 41 years, *P* = 0.01) and included more females (83% vs. 55% of patients, *P* = 0.01) but were not significantly more responsive to medications than patients with other types of epilepsy (*P* = 0.18). The disease duration was similar in the two groups (*P* = 0.44). Among the patients with non-JME epilepsy, 36 (26%) had temporal lobe epilepsy, 60 (43%) had focal extra-temporal epilepsy, 25 (18%) had primary generalized epilepsy, and in 17 patients (12%) the type of epilepsy was difficult to define.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All, n=161 (100%)</th>
<th>JME, n=23 (14%)</th>
<th>Non-JME, n=138 (86%)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean range)</td>
<td>40 (18–83)</td>
<td>33 (19–82)</td>
<td>41 (18–83)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>95 (59)</td>
<td>19 (83)</td>
<td>76 (55)</td>
<td>0.0127*</td>
</tr>
<tr>
<td>Drug resistant, n (%)</td>
<td>71 (44)</td>
<td>7 (30)</td>
<td>64 (46)</td>
<td>0.1788</td>
</tr>
<tr>
<td>Average duration of epilepsy, years</td>
<td>17.4</td>
<td>17.0</td>
<td>17.5</td>
<td>0.4375</td>
</tr>
</tbody>
</table>

*P* < 0.05

JME = juvenile myoclonic epilepsy

**WS IN JME AND NON-JME EPILEPSY PATIENTS**

Among the patients with JME, more than half (13, 57%) had WS, while less than one-third (42, 30%) of the patients with non-JME epilepsy had WS [Figure 1A, *P* = 0.01]. A logistic regression model for WS prediction, with type of epilepsy and sex as covariates, was statistically significant (chi-square 7.8 (df = 2), *P* = 0.02). We found that the type of epilepsy predicted WS and explained 6.5% (Nagelkerke R square) of the variance in WS. Patient sex was not found to significantly predict WS in this model.

Next, we compared the rates of WS in responsive and resistant JME patients [Figure 1B]. Of note, 5 of the 8 drug-responsive JME patients with WS had occasional myoclonus seizures and 4 of the 8 patients had no WS. No significant difference was found between WS in drug-responsive and drug-resistant JME (*P* = 0.3).

**Figure 1.** WS in drug-responsive and drug-resistant JME and non-JME patients

JME = juvenile myoclonic epilepsy, WS = withdrawal seizure

[A] Percentage of WS in JME and non-JME groups of patients

[B] WS in drug-responsive and drug-resistant JME patients

[C] WS in drug-responsive and drug-resistant non-JME patients
We also compared the rates of WS in responsive and resistant non-JME patients [Figure 1C]. No statistically significant difference was found in having WS between the drug-responsive patients with JME and with non-JME epilepsy \((P = 0.15)\). However, drug-resistant JME patients had significantly more WS than their counterparts with non-JME epilepsy \((P = 0.02)\).

Ten patients had more than one event of WS: seven had two WS, and one patient each had three, four, and five WS. Only two of these patients had drug-resistant (non-JME) epilepsy. All other patients had drug-responsive JME (4 out of 9 patients) or non-JME (4 out of 24) epilepsy \((P = 0.1)\). The patients who had three and five WS were drug-responsive JME patients and the patient with four WS was drug-responsive non-JME.

The medications that were discontinued or their dose was reduced prior to WS are depicted in Figure 2. Valproic acid (VPA) was discontinued in 7 of 13 (54%) of JME patients with WS and in only 8 of 42 (19%) of non-JME epilepsy patients \((P = 0.01)\). Among the 7 JME patients who discontinued VPA, 6 (86%) were females, while in the non-JME patient group 4 of 8 (50%) were females.

TIME FROM THE ASM DISCONTINUATION TO WS
Almost two-thirds (32, 58%) of the patients had WS up to one week from the discontinuation or dose reduction of the drug, while others had WS between 2 weeks to 9 years following the ASM cessation (for periods of more than 1–2 weeks, the exact duration from discontinuation to WS was usually less precise due to incomplete documentation).

REASON FOR THE ASM DISCONTINUATION
The reason for drug discontinuation was patient non-adherence to medications in 39 cases and physician-guided drug changes in 16 cases. The distribution of these reasons among the various groups of patients is depicted in Figure 3. No significant difference in the cause of ASM discontinuation was found between JME and non-JME patients [Figure 3A] \((P = 0.9)\) or between drug-responsive and drug-resistant patients in general [Figure 3B] \((P = 0.8)\) in the JME \((P = 0.8)\) and non-JME \((P = 0.9)\) groups separately.

DISCUSSION
We found that the patients with JME had more WS than patients with other epilepsies. Although there was a trend of patients with JME being more drug-responsive, our finding cannot
be explained by discontinuation of antiepileptic medications in drug-responsive cases alone, since drug-resistant JME patients had significantly more WS than those with other types of drug-resistant epilepsy. However, drug-responsive JME patients may also have a greater tendency for loss of seizure control following ASM withdrawal, since there was a trend toward drug-responsive JME patients having two or more WS more frequently than their non-JME counterparts. This finding could be explained by a higher expression of impulsive personality traits in JME patients [10].

The fact that patients with JME were younger than patients with other types of epilepsy may explain at least in part the higher WS rate in this population, since a greater tendency for non-adherence was described in this group [11]. However, another possible explanation for the difference in WS between JME and non-JME epilepsy patients may be a greater sensitivity of JME to drug withdrawal. This suggestion is in line with previous clinical observations [12] and may reflect the general sensitivity of JME to various factors such as sleep deprivation, alcohol use, and flickering lights [13]. The sensitivity of JME to WS may be especially pronounced when the discontinued or replaced ASM is VPA, which has been reported to be more efficacious than other medications in primarily generalized epilepsies in general [14] and particularly in JME [15].

Although not significantly affecting the risk for WS, there was a larger proportion of females among the JME than among the non-JME patients. This finding is particularly important since women of childbearing age tend to be non-adherent to medications [16]. VPA use by women of childbearing age has recently been legally restricted by the EMA [17] due to the teratogenicity of this drug. However, withdrawal of VPA was associated with loss of seizure control in pregnant women [18], and women with JME may present with less seizure control than men due to VPA use restriction [14]. Fortunately, it has been reported that VPA’s teratogenic effects are dose-dependent [19], and that low doses of VPA may be enough to achieve seizure freedom in most patients with JME [20]. Taken together, these data suggest that a more rational and individualized approach to VPA treatment for women of childbearing age with JME is warranted rather than an automatic cessation of the drug.

Several cases of sudden unexplained death in epilepsy patients (SUDEP) were reported in JME [21-23] both in drug-resistant [21] and drug-responsive cases [23]. It is not clear whether drug withdrawal played a role in these reported SUDEP cases. However, this mechanism cannot be excluded.

LIMITATIONS

There are several limitations to this study. First, the whole cohort is rather small, especially the group of JME patients and among them the drug-resistant patients. However, even in this small group we were able to show significant results. Second, we had no information about the overall number of patients who stopped ASMs or reduced their dosage (with and without WS) and therefore we cannot directly assess the risk to have WS amongst all patients who withdrew the medications. However, the main scope of the present work was to characterize the patients who had WS. Last, we did not have exact data on the pace of drug discontinuation, although it can be speculated that patient non-adherence was quite abrupt, whereas physician-guided withdrawal was gradual. However, we found no significant effect of the initiator of the discontinuation on the rates of WS in the various groups of patients. The implication of the pace of drug discontinuation on the induction of WSs and the time when no WS is to be expected after ASM discontinuation in different types of epilepsy warrant further prospective research.

CONCLUSIONS

Both drug-responsive and drug-resistant JME patients are prone to WS. Physicians should inform patients with JME about the high sensitivity of this epilepsy type to ASM withdrawal and emphasize the importance of adherence to treatment, including mitigating the possible risk of SUDEP. Special attention should be paid to the population of women of childbearing age for whom the decision of VPA treatment cessation should be individualized to each case, and careful schedules of switch from VPA to other ASMs should be implemented.

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References

The use of lipid-formulated RNA vaccines for cancer inflammatory responses in humans that were not predicted from preclinical studies. Tahtinen and colleagues showed inflammation in a host-specific manner. In human immune the broad spectrum of pro-inflammatory cytokines (including associated innate signaling, an effect that was unexpectedly amplified by certain lipids used in vaccine formulations reduce activation of Toll-like receptor signaling.

Olson and colleagues used a case-control, test-negative design to assess vaccine effectiveness against COVID-19 resulting in hospitalization, admission to an intensive care unit (ICU), the use of life-supporting interventions (mechanical ventilation, vasopressors, and extracorporeal membrane oxygenation), or death. Between 1 July and 25 October 2021, a total of 445 case patients and 777 controls age 12–18 years were enrolled. Overall, 17 case patients (4%) and 282 controls (36%) had been fully vaccinated. Of the case patients, 180 (40%) were admitted to the ICU and 127 (29%) required life support. Only 2 patients in the ICU had been fully vaccinated. The overall effectiveness of the BNT162b2 vaccine against hospitalization for COVID-19 was 94% (95% confidence interval [95%CI] 90–96); the effectiveness was 95% (95%CI 91–97) among test-negative controls and 94% (95%CI 89–96) among syndrome-negative controls. The effectiveness was 98% against ICU admission and 98% against COVID-19 resulting in the receipt of life support. All 7 deaths occurred in patients who were unvaccinated. The authors conclude that among hospitalized adolescent patients, two doses of the BNT162b2 vaccine were highly effective against COVID-19-related hospitalization and ICU admission or the receipt of life support.

The secret of joy is the mastery of pain.
Angela Anais Juana Antolina Rosa Edelmira Nin y Dulmell (Anais Nin) [1903–1977], French-Cuban-American diarist, essayist, novelist and writer of short stories and erotica

**Effectiveness of BNT162b2 vaccine against critical COVID-19 in adolescents**

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**IL-1 and IL-1ra are key regulators of the inflammatory response to RNA vaccines**

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