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Impulsivity traits in eyelid myoclonia with absences

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ABSTRACT

Purpose: Eyelid myoclonia with absences (EMA) shares some clinical characteristics with juvenile myoclonic epilepsy (JME), in which impulsivity traits have been described. Aim of the study was to evaluate whether EMA patients could present a peculiar behavioural profile.

Methods: Patients with EMA, JME and healthy controls (HCs) were enrolled. Subjects with intellectual quotient <80 were excluded from the study. All the enrolled subjects underwent the Italian version of the Barratt Impulsiveness Scale (BIS-11) and the three dimensions of impulsivity (motor, attentional-cognitive and non-planning impulsivity) were considered.

Results: Seventeen patients with EMA (12 females [70.6%], age 30.8±10 years), 29 patients with JME (17 females [58.6%], age 29.1±9.7 years) and 31 HCs (15 females [48.4%], age 27.6±5.8 years) were enrolled. Both EMA and JME patients presented a borderline significantly higher BIS total score than HCs (p=0.064). EMA patients presented a significantly higher BIS nonplanning subscore than JME patients and HCs (p=0.001).

Conclusion: The study showed the presence of peculiar behavioral characteristics in EMA patients, slightly different from patients with JME.

Introduction

The construct of *"impulsivity"* is the predisposition to act towards unplanned and immediate reactions to different stimuli without considering the possible negative consequences to themselves or the others related to these reactions [1]. Interestingly, pathological impulsive behaviour has been associated with several risky actions, including aggression, conduct disorder, drug addiction and suicide attempts [2]. Enhanced impulsivity traits have been reported in patients with juvenile myoclonic epilepsy (JME) [3], as confirmed by a recent meta-analysis reporting that cognitive impulsivity with impaired response inhibition is consistently observed in these patients [4]. The study of personality in patients with idiopathic generalized epilepsy (IGE) may have important implications for the therapeutic management and prognostic evaluation of these patients. In fact, some studies demonstrated that a higher expression of impulsive traits could be associated with worse seizure control in JME patients, linking impulsivity to a more severe phenotype [5].

Eyelid myoclonia with absences (EMA) is an age-related epilepsy syndrome characterized by the presence of different seizure types in combination, such as absences, eyelid myoclonia and generalized tonic-clonic seizures [6]. EMA could be considered an IGE, but in the last classification of epilepsies [7], despite multiple descriptions as a separate nosological entity among IGE [6,8,9], it has not been recognized as a distinctive epilepsy type and is frequently misclassified as a clinical subtype of JME.

Considering EMA as an epileptic syndrome with high levels of drug resistance [8], the evaluation of all the associated factors may be useful for a better clinical approach in these patients. The neuropsychological profile of EMA has been described as normal [10], except for a small subgroup of patients showing intellectual disability [11]. However, in one study, even in patients with a normal intelligence quotient (IQ), borderline impairment of cognitive abilities was found in a sample of paediatric patients [12]. Nevertheless, unlike JME, with regard to personality profile, nothing has been reported in EMA patients, and impulsiveness should be of interest.

The aim of our study was to evaluate the presence of impulsivity traits in patients with EMA compared to patients with JME and a group

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of healthy controls (HCs).

Material and methods

Study design

The present is an observational study developed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [13] (Supplement 1).

Study population

We selected all patients with a diagnosis of EMA and JME [6,14,15] made according to the most recent criteria, consecutively ascertained as outpatients of the epilepsy centre of the University of Catania between February 2019 and February 2020. In particular, the diagnosis of EMA was made according to the following clinical criteria: frequent occurrence of eyelid myoclonia with or without absences; generalized epileptiform activity triggered by eye closure; generalized photoparoxysmal EEG response; or a history of visually induced seizures [6, 15]. The diagnosis of JME was made in patients presenting myoclonic jerks without loss of consciousness occurring on or after awakening and associated with typical generalized epileptiform EEG abnormalities [14]. A group of HCs with no neurological or psychiatric disorders was recruited. Subjects affected by major psychiatric disorders, including unipolar depression, bipolar disorder, anxiety disorders, psychosis, impulse control disorders, and substance abuse, were excluded from the study. To exclude patients with major psychiatric conditions, the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders Axis I (SCID-I) was performed. Patients taking neuroleptics, antidepressants and/or benzodiazepines were excluded from the study. All enrolled subjects underwent the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) to exclude individuals with an IQ less than 80.

The following clinical variables were considered for patients: sex, age, education, age at seizure onset, family history of epilepsy, disease duration, and presence in their history of photosensitivity and eye closure sensitivity. Moreover, the impact of the different antiseizure medications (ASMs) taken by the patients at the last follow-up visit was evaluated. For HCs, sex, age and education years were recorded. The study was approved by the Ethics Committee of the University Hospital "Policlinico-San Marco" of Catania. All enrolled subjects signed written informed consent forms.

Instrument

The Italian version of the Barratt Impulsiveness Scale (BIS-11) [16] was used to assess self-reported impulsivity.

The BIS-11 is the most widely used self-administered questionnaire for impulsivity evaluation; it is composed of 30 items measured on a four-point ordinal scale (1 = Rarely/Never, 2 = Occasionally, 3 = Often, 4 = Almost Always/Always). "Impulsivity" can be considered both an overall construct and categorized into three dimensions: motor impulsivity (acting without thinking), attentional-cognitive impulsivity (immediate cognitive decision-making and set-shifting) and nonplanning impulsivity (decreases in orientation and planning of the future). Although there is no "normality" cut-off value, higher scores indicate higher self-reported impulsivity.

Statistical analysis

All data were collected in an ad hoc created database. Data cleaning was performed before the data analysis. Qualitative variables are described as percentages, and quantitative variables are described as the mean ± standard deviation (SD). The data were examined for normality using the Shapiro-Wilk test. Pearson's chi squared tests (χ^2) or two-tailed Fisher's exact tests were used to study categorical variables; unpaired t tests or ANOVAs for parametric data or Mann-Whitney tests for nonparametric data were used for comparisons. The Bonferroni correction for multiple comparisons was applied when appropriate. A stepwise backward multivariate linear regression was applied to identify factors associated with differences in BIS scores, using variables with $p<0.20$ in univariate calculations. A $p<0.05$ was set as the level of significance.

Data were analysed using the STATA 16 software package (version 16.0, College Station, TX).

Table 1
Demographic and clinical features of patients.

Variables	EMA patients, *n.* 17	JME patients, *n.* 29	HC, *n.* 31	*p* value
Females, *n.* (%)	12 (70.6)	17 (58.6)	15 (48.4)	0.324
Age, years	30.8±10	29.1±9.7	27.6±5.8	0.453
Education, years	11.6±3	11.6±3	12.9±3.2	0.216
Age at disease onset, years	11.5±3.2	13.8±5.5	/	0.03
Disease duration, years	15.5±11.4	12.6±9.2	/	0.50
Seizure types in the history				
GTCS	17 (100)	29 (96.5)	/	1
Limb myoclonia	10 (58.8)	29 (100)	/	<0.001
Absences	15 (88.2)	10 (34.5)	/	0.001
Eyelid myoclonia	17 (100)	1 (3.4)		<0.001
Family history, *n.* (%)	9 (52.9)	9 (31)	/	0.14
Photosensitivity, *n.* (%)	15 (88.2)	14 (48.3)	/	0.01
Eye closure sensitivity, *n.* (%)	15 (88.2)	2 (6.9)	/	<0.001
Seizure freedom	7 (41.2)	15 (51.7)	/	0.49
Drug resistance	5 (29.4)	4 (13.8)	/	0.26
Polytherapy	7 (41.2)	8 (27.6)	/	0.52
ASMs, *n.* (%)				
Clobazam	3 (17.6)	1 (3.4)	/	0.13
Lamotrigine	2 (11.8)	7 (24.1)	/	0.45
Levetiracetam	13 (76.5)	18 (62.1)	/	0.35
Perampanel	2 (11.8)	1 (3.4)	/	0.54
Phenobarbital	0	2 (6.9)	/	0.52
Topiramate	3 (17.6)	1 (3.4)	/	0.13
Valproate	4 (23.5)	12 (41.4)	/	0.34
Zonisamide	0	1 (3.4)	/	1
Drugs withdrawal	0	2 (6.9)	/	0.52
BIS total score	60.5±12.9	57.6±7.2	54.2±7.6	0.064
BIS motor score	18.1±5.4	19.3±3.3	18.2±3.5	0.471
BIS attention score	15.5±4.3	15.6±3.2	14.4±2.6	0.321
BIS non-planning score	26.9±5.2	22.7±5.0	21.6±3.7	0.001* **

Legend: values are expressed as mean±standard deviation and number and percentage. N, number; ASMs, antiseizure medications. EMA, eyelid myoclonia with absences; JME, juvenile myoclonic epilepsy; HC, Healthy controls. BIS, Barratt impulsiveness scale. Bold values indicate significance after Bonferroni correction. *= EMA patients versus JME patients; **= EMA patients versus HCs.

Results

Seventeen patients with EMA, 29 patients with JME and 31 HCs were enrolled. The demographic and clinical characteristics are described in Table 1. Age at onset of epilepsy and limb myoclonia frequency were lower in EMA patients than in JME patients; moreover, photosensitivity, eye closure sensitivity, eyelid myoclonia and absences were significantly more frequent in patients with EMA.

BIS total score and subscores

As detailed in Table 1, both EMA and JME patients presented a borderline significantly higher BIS total score than HCs ($p=0.064$). A statistically significant difference was evident when comparing the BIS

Table 2
Univariate and multivariate analyses in EMA and JME patients as regard to BIS non-planning scores.

Variables	Univariate analysis			Multivariate analysis		
	Coefficient	95% CI	*p* value	Coefficient	95% CI	*p* value
Group (EMA or JME)	4.1	0.9–7.3	0.01	3.6	0.5-6.62	0.023
Sex (females)	2.1	−1.3–5.5	0.23			
Age	0.05	−0.1–0.2	0.59			
Education years	−0.09	−0.66–0.49	0.77			
Age at disease onset	0.15	−0.19–0.48	0.39			
Disease duration	0.02	−0.2–0.2	0.79			
Family history	2.1	−1.2–5.4	0.21			
Photosensitivity	3.4	0.04–6.6	0.05			
Eye closure sensitivity	2.3	−1–5.7	0.17			
History of GTCS	1.8	−13–9.4	0.75			
Seizure freedom	1.3	−1.9–4.6	0.42			
Drug resistance	0.004	−0.04–0.06	0.87			
ASMs						
Clobazam	−3	−8.7–2.7	0.29			
Lamotrigine	−0.9	−5–3.2	0.67			
Levetiracetam	4.4	1.2–7.6	0.008	3.9	0.8-7	0.01
Phenobarbital	−4.9	−12.8–2.9	0.21			
Topiramate	−0.5	−6.3–5.2	0.85			
Valproate	−2.9	−6.3–0.4	0.08			
Drugs withdrawal	−4.4	−12.3–3.4	0.26			

Legend: CI, confidence intervals; SD, standard deviation; EMA, eyelid myoclonia with absences; JME, juvenile myoclonic epilepsy; BIS, Barratt impulsiveness Scale; GTCS; generalized tonic clonic seizures; ASMs, antiseizure medications. Bold values indicate significance.

nonplanning subscores of the three groups (p=0.001).

Analysing only patients with epilepsy, no significant differences were recorded when comparing EMA patients and JME patients in terms of BIS total score, BIS motor score and BIS attention score. However, EMA patients presented a significantly higher BIS nonplanning score than JME patients (p=0.01).

In the multivariate analysis, the association between EMA and higher BIS nonplanning subscores was confirmed (Coeff=3.6, 95% CI=0.5–6.6; p=0.023). Moreover, levetiracetam (LEV) intake was found to be independently associated with higher BIS nonplanning subscores (Coeff=3.9, 95% CI=0.8–7; p=0.01) (Table 2).

Discussion

In our study, patients with epilepsy presented higher levels of impulsivity than HCs. Interestingly, patients with EMA had a significantly higher BIS score regarding planning abilities than patients with JME, patients already known for their impulsivity [3,17].

In fact, several studies have assessed the psychological characteristics of JME, historically called *impulsive petit mal*. In particular, it has been reported that the personality traits of JME patients are characterized by immature and impulsive elements, propensity to impulse control disorders, socially inconvenient conduct and novelty-seeking temperament [18,19]. These psychological characteristics were found to be associated with both cognitive impairment, particularly in executive functioning and attention, and drug resistance [5,20]. Interestingly, even though "impulsivity" has been classically interpreted as a "behavioural disturbance", it is now considered a "multidimensional" construct, not necessarily related to psychiatric disturbances but reflecting some degree of cognitive impairment in terms of attentional control, concentration, planning and deliberate reasoning [21]. From a pathophysiological point of view, the "inhibitory" impairment, typical of JME, could be linked to the alterations described in mesiofrontal and frontobasal regions, as well as in other limbic and paralimbic areas, which are related to impulsivity and social behaviour [22]. In fact, the increased functional connectivity between the motor system and the frontoparietal cognitive networks has been well described in JME, as demonstrated by different studies with multiple neuroimaging techniques [23]. This hyperconnectivity between motor and nonmotor areas may explain why some physiological processes, such as cognitive activities, photosensitivity or eye closure sensitivity, can precipitate myoclonia in some patients with JME [24]. On some level, although in EMA, the main impaired pathway is represented by the occipital-frontal network, abnormalities in the mesial frontal regions and fronto-opercular cortex have also been reported [8,25].

These latter alterations, shared with JME, can allow us to speculate that the involvement of similar circuits could be responsible for the higher levels of impulsivity found in both syndromes.

An interesting finding was the independent association of LEV use with higher levels of nonplanning impulsivity in EMA patients. However, it has already been shown that LEV use can exert a negative psychotropic effect, with increases in aggression and loss of self-control, especially in subjects with pre-existing higher non-planning impulsiveness [26]. This effect seems to be confirmed in our sample of EMA patients.

We are aware that some limitations should be considered when interpreting our findings. The small sample size, primarily related to the low frequency of EMA in the general population, could limit the power of the study. Moreover, the exclusion of those patients with intellectual disability could interfere with the generalizability of our results. Furthermore, although the Italian version of the BIS-11 is considered a reliable psychometric instrument, presenting good internal consistency (Cronbach's α=.79) and two-month test-retest reliability (r=.89), limited to some subdomains, a low internal consistency, probably due to translation or cultural "discrepancies", has been observed [16]. However, it should be emphasized that the subdomain "nonplanning impulsiveness" has been reported as the only subdomain in the Italian version that "fully reproduced" the English version [16]. Finally, the lack of a "comprehensive" evaluation of executive-attentional functioning did not allow us to assess possible associations between impulsivity and cognitive control deficits.

In conclusion, the findings of our study showed the presence of enhanced impulsivity in EMA patients, with some peculiar differences compared to patients with JME. Together with the typical electrophysiological [9,25], clinical and prognostic features [8], the present results could contribute to a necessary better definition of EMA.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.07.006.

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