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Conference paper

EFFECTS OF MUSIC ON SEIZURE FREQUENCY IN INSTITUTIONALIZED SUBJECTS WITH SEVERE/PROFOUND INTELLECTUAL DISABILITY AND DRUG-RESISTANT EPILEPSY

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SUMMARY

Background: *Approximately one-third of patients with epilepsy continue to experience seizures despite adequate therapy with antiepileptic drugs. Drug-resistant epilepsy is even more frequent in subjects with intellectual disability. As a result, several non-pharmacological interventions have been proposed to improve quality of life in patients with intellectual disability and drug-resistant epilepsy. A number of studies have demonstrated that music can be effective at reducing seizures and epileptiform discharges. In particular, Mozart's sonata for two pianos in D major, K448, has been shown to decrease interictal EEG discharges and recurrence of clinical seizures in patients with intellectual disability and drug-resistant epilepsy as well. The aim of this study is to investigate the influence of Mozart's music on seizure frequency in institutionalized epileptic subjects with profound/severe intellectual disability.*

Subjects and methods: *Twelve patients (10 males and 2 females) with a mean age of 21.6 years were randomly assigned to two groups in a cross-over design; they listened to Mozart K448 once a day for six months.*

Results: *A statistically significant difference was observed between the listening period and both baseline and control periods. During the music period, none of the patients worsened in seizure frequency; one patient was seizure-free, five had a greater than 50% reduction in seizure frequency and the remaining showed minimal (N=2) or no difference (N=4). The average seizure reduction compared to the baseline was 20.5%. Our results are discussed in relation to data in the literature considering differences in protocol investigation.*

Conclusions: *Music may be considered a useful approach as add-on therapy in some subjects with profound intellectual disability and drug-resistant epilepsy and can provide a new option for clinicians to consider, but further large sample, multicenter studies are needed to better understand the characteristics of responders and non-responders to this type of non-pharmacological intervention.*

Key words: *drug-resistant epilepsy - Mozart effect - music - intellectual disability*

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INTRODUCTION

Despite the continued introduction of new antiepileptic drugs (AEDs) in clinical practice, drug therapy is ineffective in a large proportion of subjects suffering from epilepsy, with percentages ranging from 6 to 69%, (Téllez-Zenteno et al. 2014). The wide variability appears to be supported by a number of factors, in particular the discrepancy in the definition of AED's effectiveness criteria and differences due to the type of patient population examined. The definition of efficacy criteria appears to be controversial for several reasons; this controversy has given rise to terminological differences such as "medically intractable", "refractory", "pharmacoresistant" and "drug-resistant" epilepsy. As a result, the International League against Epilepsy (ILAE) has proposed a consensus conference suggesting the use of the term "drug-resistant epilepsy" (DRE) as "failure of adequate trials of two tolerated and properly selected and utilized AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al. 2010). In the first place, when considering this definition, the effectiveness of therapy is associated with the absence of a seizure. In addition, a one-year observation period is recommended, or an interval without seizures that is at least triple the prior inter-seizure interval.

There is still considerable disagreement in the literature regarding the incidence and prevalence of DRE, and the available data should be analyzed considering the population type being examined. Epidemiological data indicate that 20-30% of patients with a new diagnosis of epilepsy will have a DRE. The frequency of epilepsy and DRE in particular remains higher in subjects with intellectual disability (ID), a population where a direct relationship between the severity of ID and the presence of DRE has been previously documented (Robertson et al. 2015). The coexistence of ID and DRE is also burdened with a negative prognosis quoad valetudinem (quality of life, risk of physical trauma and coexisting pathologies) as well quoad vitam (premature and sudden death), together with obvious problems of a diagnostic and therapeutic nature (Doran et al. 2016, Kwan et al. 2010).

The presence of DRE in subjects with ID has therefore strongly stimulated research on new and innovative approaches to intervention, the effectiveness of which are still the subject of further investigation (Jackson et al. 2015). In particular, in the absence of effective pharmacological and surgical therapies, non-pharmacological interventions are currently playing an increasing role. Among the so-called "complementary" treatments, the utilization of music in several nervous system disorders such as parkinsonism, dementia, aphasia, and autism has given rise to "neurologic music therapy" (D'Alessandro 2016, Schlaug et al. 2010, Thaut et al. 2015). With regards to epilepsy, the most significant results were obtained by listening to the music of Mozart (Lin et al. 2011b). Despite initial skepticism, the phenomenon in question, initially referred to as the "Mozart effect" (Rauscher et al. 1993), received numerous confirmations from clinical, neurophysiological and functional neuroimaging investigations (Bodner et al. 2001). A first reporting of the effect on epileptic patients dates back to 1998 (Hughes et al. 1998). Subsequent investigations have documented the influence of Mozart's music both instrumentally as well as clinically (Lin et al. 2010; Turner 2004). According to a recent meta-analysis, a reduction in interictal epileptic discharges appears to be significant in 84% of patients and is particularly evident in patients with idiopathic epilepsy and with generalized or central discharges, and in patients with a higher intelligence quotient (Dastgheib et al. 2014). In addition, a reduction in seizure frequency has been described in a series of anecdotal observations and in a number of clinical investigations (Lahiri & Duncan 2007; Lin et al. 2014a), some of which also included subjects affected by DRE (Bodner et al. 2012; Coppola et al. 2015; Lin et al. 2011a).

The effect of listening to music therefore appears promising, but the available data is still numerically insufficient and subject to methodological criticism. In this study, institutionalized subjects with multiple disabilities and concomitant DRE were examined with the goal of broadening the current research on the topic.

SUBJECTS AND METHODS

Subjects

The study was conducted at the Serafico Institute in Assisi (Italy), a specialized inpatient facility providing rehabilitation services to 72 individuals with multiple disabilities, primarily of an intellectual and sensorimotor nature. All residents receive a highly personalized multidisciplinary program of rehabilitative and educational interventions. Extensive clinical documentation regarding diagnosis is required prior to admission. In the case of epileptic seizures, documentation must include proof of a previous hospital stay at a centre recognized by the Italian League against Epilepsy (LICE) specialized in the diagnosis and treatment of epilepsy.

The initial sample size consisted of 16 subjects with a diagnosis of DRE according to ILAE criteria. Of this initial sample, four subjects were excluded for deafness, reflex epilepsy, severe behavioural disorders, as well as for discontinuity in AED therapy. The final sample size consisted of 12 subjects (10 males and 2 females) with an average age of 21.6 +/-9.6 (range 5–39) years. All individuals suffered from symptomatic epilepsy; each experienced more than one seizure per month for the six months prior to the onset of the study and assumed at least two AEDs. The AED schedule remained unaltered throughout the data collection period. The mean number of AEDs was 3.2 (range 2-6). All subjects had severe/profound intellectual disability according to Vineland Adaptive Behaviour Scales criteria (Carter et al. 1998). The clinical and demographic characteristics of each patient are summarized in Table 1.

Methods

The 12 patients were randomly assigned in the control or treatment group by randomly generated even (for treatment) and uneven (for control) numbers utilizing a computer program (www.random.org). Stratification for age, sex, and clinical characteristics was not carried out. The study protocol lasted for 12 months using a cross-over design between the two groups as follows: subjects of group A received treatment first for a six-month period and subsequently received no treatment in the following six-month period, and vice versa for the subjects of group B. This 12-month study phase was preceded by a six-month observation period to establish baseline seizure frequency for each subject. Total observation period was 18 months. Consistent with the methodology proposed by Lin et al. (2011a), the treatment group listened to Mozart's sonata for two pianos in D major, K448, once a day for six months. The effectiveness of treatment was rated as: seizure-free (100% remission), very good (>50% decrease in seizure frequency), minimal (25-50% decrease in seizure frequency), unmodified (from 25 to -25% change in seizure frequency), worsened (>25% increase in seizure frequency) with respect to baseline. Since all individuals were unable to give informed consent, written informed consent was obtained from parents or legal guardians of the participants enrolled in the study. The protocol was approved by the Ethics Committee of the Serafico Institute and by CEAS Umbria (the region's health care ethics committee).

Statistical Analysis

Data on seizure frequency are expressed in means, standard deviations and range. We have also calculated percentage reduction in seizure frequency after music listening. Since data distribution was not normal, in order to compare the difference in the number of seizures before, during and after the period with music listening the non parametric Wilcoxon test was applied. A p value <0.05 was considered significant. Statistical Analysis was performed by SPSS 20.0 (SPSS for Windows, Version 20.0 IBM, New York, USA).

Table 1. Demographic and clinical characteristics of patients

Patient	Sex	Age (years)	ID	Epilepsy classification	Seizure type	EEG	Brain MRI	Seizure frequency*	DRE duration (years)	AED therapy
1	M	23	Severe	Symptomatic	Focal and generalized	Left frontal focus	Bihemispheric frontal damage; brain atrophy	150	17	VPA+TPM+ PB+BDZ
2	M	31	Severe	Symptomatic - tuberous sclerosis	Focal and generalized	Left temporal focus	Multiple calcifications; brain atrophy	30	30	VPA+LTG
3	M	39	Profound	Symptomatic	Focal and generalized	Left fronto-temporal focus	Brain atrophy	511	38	LTG+PB+LCM+ CLO+LEV+BDZ
4	M	5	Profound	Symptomatic - severe head injury	Focal and generalized	Right fronto-temporal focus	Right frontal damage	15	3	CBZ+LEV
5	F	17	Severe	Symptomatic	Generalized	Multiple foci	Periventricular leukomalacia	85	16	VPA+CLO+LEV
6	M	19	Profound	Symptomatic - MCD (inv dup 15)	Generalized	Multiple foci	Bilateral polymicrogyria	171	18	VPA+LTG+ CLO+BDZ
7	M	17	Profound	Symptomatic	Focal and generalized	Multiple foci	Periventricular leuko-malacia; brain atrophy	15	16	VPA+LEV+BDZ
8	M	22	Profound	Symptomatic - tuberous sclerosis	Focal and generalized	Left temporal focus	Left parietal cortico-subcortical calcification	21	21	VPA+LCM+ LEV+BDZ
9	F	11	Profound	Symptomatic	Focal and generalized	Multiple foci	Cortico-subcortical brain atrophy	139	10	VPA+LTG+BDZ
10	M	18	Severe	Symptomatic	Focal and generalized	Right temporal focus	Left hemispheric atrophy	78	15	VPA+RFN+PB
11	M	22	Severe	Symptomatic	Focal and generalized	Left frontal focus	Periventricular leuko-malacia; brain atrophy	294	12	PB+LEV
12	M	35	Severe	Symptomatic – PHIE	Focal and generalized	Multiple foci	Brainstem atrophy	15	28	VPA+OXC

ID: Intellectual Disability (Vineland Adaptive Behavior Scale classification); DER: drug-resistant epilepsy; *: baseline average monthly frequency; EEG, electroencephalogram; MRI: magnetic resonance imaging; MCD: malformation of cortical development; PHIE: preterm hypoxic - ischemic encephalopathy; AED: antiepileptic drug; BDZ: benzodiazepine; CBZ: carbamazepine; LCM: lacosamide; LEV: levetiracetam; PB: phenobarbital; LTG: lamotrigine; OXC: oxcarbazepine; VPA: valproic acid; TMP: topiramate; RUF: rufinamide

RESULTS

Data analysis (Figure 1, Table 2) illustrates that the average seizure reduction compared to the baseline was 20.5% during the treatment phase. Overall, 50% of the subjects in the study exhibited a very good response to treatment. None of the patients worsened in seizure frequency; one patient was seizure-free, five obtained a greater than 50% reduction in seizure frequency, and the remaining showed minimal (N=2) or no difference (N=4). Statistical analysis revealed a treatment effect: significant differences existed between treatment and baseline periods (p=0.009) as well as the control period (p=0.003). No statistically significant difference was observed between baseline and control periods, indicating that treatment effect did not persist over time. Moreover, there did not appear to be any effects due to the different periods of music exposure in the two study groups. With respect to clinical and demographic characteristics, no statistically significant difference was observed between patients who exhibited a different response to treatment. In this regard, it is likely that small group size may have prevented the detection of any possible differences. Nevertheless it is interesting to note that the two groups of responders and non-responders differed in baseline seizure frequency (52.7±-54.5 vs 201.3±-178.5, respectively) suggesting a possible contribution of the degree of disease severity.

Table 2. Average monthly seizure frequency during study phases (six months with and six months without music listening)

Group		Study phases		Significance
A		with music	without music	
	x	119.8	158	p=0.046
	DS	159.8	166.3	
	range	1-417	0-463	
B		without music	with music	
	x	93	82	p=0.028
	DS	111.4	111.9	
	range	13-298	6-296	

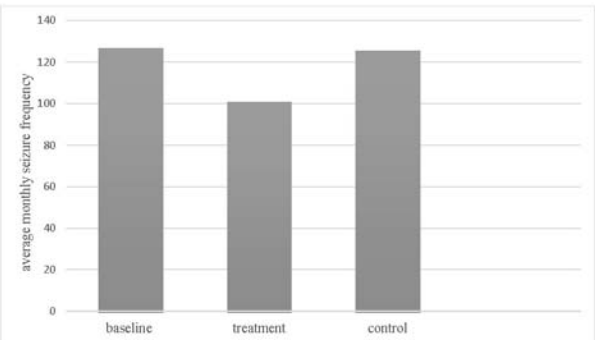

Figure 1. Seizure frequency during music treatment compared to baseline and control period. Treatment vs baseline: p=0.009; treatment vs control: p=0.003; baseline vs control: no significant differences

DISCUSSION

The study was conducted on subjects with drug-resistant epilepsy who, given the severity of their intellectual disability, have been institutionalized. In the absence of efficacy of drug therapy with AEDs, attempts were made to verify the usefulness of non-pharmacological treatment based on listening to music. The study was conducted randomly utilizing a cross-over design on a very homogeneous group of institutionalized patients and carefully monitored from a clinical standpoint. In fact, in the population studied, Mozart's sonata K448 was able to significantly reduce seizure frequency. Previous studies examining subjects with DRE associated with disabling neuropsychiatric disorders revealed similar results. Lin et al. (2011a) observed a 53.6% reduction in seizure frequency; 72.7% of subjects (n= 11) demonstrated a greater than 50% reduction, including 18.9% who were seizure-free. Coppola et al. (2015) observed a 51.5% reduction in seizure frequency and 45.4% of subjects who benefited from the intervention, but in their sample of 11 subjects no seizure-free cases were detected. Moreover, in the two weeks following the end of the treatment, a 20.7% reduction in seizure frequency was documented. In a randomized controlled trial of 25 subjects, Bodner et al. (2012) observed a 24% reduction in seizure frequency, with 80% of subjects benefitting from the intervention, and 24% of subjects who were seizure-free. In a one-year follow-up study, the effect persisted with a 33% overall reduction. In our investigation of 12 subjects, we observed a 20.5% reduction in seizure frequency; 50% of patients demonstrated a positive response to treatment, including 8% who were seizure-free. However, in the six months following the treatment the beneficial effect was lost.

Numerous justifications can support the differences in results, in particular regarding the various treatment protocols implemented. Our protocol as well as that of Lin et al. (2011a) called for listening to Mozart once a day for a six-month period. Coppola et al. (2015) presented a treatment protocol of two hours daily for a 15-day period (furthermore, in this study a fixed set of Mozart's music was selected and electronically edited in order to filter the frequencies). Bodner et al. (2012) based their study on a nighttime protocol with regular listening intervals of 8.5 minutes per hour for a one-year period.

In any case, it is important to remember that epilepsy is a dynamic phenomenon and presents spontaneous fluctuations in seizure frequency. The variables that can influence the course of the disease are numerous (Piccirilli 1994). The outcome is therefore difficult to evaluate in an accurate manner. Previous investigations have repeatedly reported the possible role of occipital localization of epileptic discharges (Coppola et al. 2015; Lin et al. 2011b). From this perspective, our population appears to be very homogeneous and thus does not allow for this kind of difference to be detected.

In our study, differences in clinical and demographic characteristics cannot justify the differences in the effects of treatment. The only possible justification that can be derived from the different responses of the subjects can be inferred from the average monthly baseline seizure frequency data recorded (Figure 2). However, these findings refer to subjects with DRE and obviously cannot be generalized. To look for the differential characteristics between responders and non-responders, however, seems extremely important. At the moment this issue appears difficult to resolve given the limitations inherent in these types of studies. Multicenter investigations would be clearly more capable of evaluating a larger group of patients and classifying them according to the many individual variables involved. In this perspective, very interesting preliminary data suggest that some qEEG markers are able to identify subjects potentially sensitive to the positive effect of Mozart's music (Lin et al. 2014b).

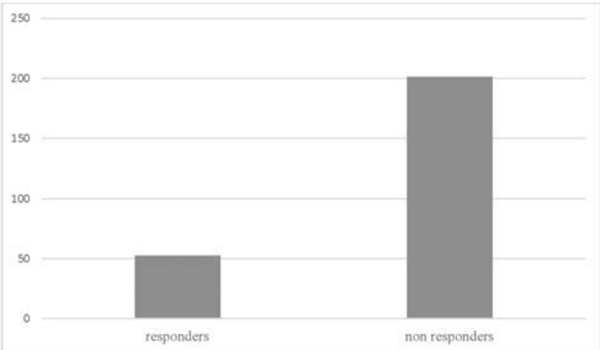

Figure 2. Average monthly baseline seizure frequency in responders and non responders

CONCLUSION

Listening to Mozart's music appears to produce a significant reduction in seizure frequency in epileptic subjects where AED therapy has proven ineffective. Clinical, neurophysiological and experimental investigations corroborate the efficacy of this non-pharmacological treatment in epileptic subjects (Lin et al. 2010, 2012, 2013b) despite the small sample sizes examined and methodological differences utilized. The hypotheses regarding the mechanism of action are still under discussion, but it is well known that a typical effect of a musical experience is entrainment, the phenomenon by which a musical rhythm resonates with cerebral rhythms (Ancarani 2017, Buzsaki 2006). On the other hand, differential response of brain activity to the different characteristics of musical stimuli is also well-documented (Hughes 2001; Verrusio et al. 2015) and it is well-known that music can trigger epileptic seizures (Maguire 2015). Other possible mechanisms, not incompatible with each other, call into question parasympathetic system stimulation (Lin et al. 2013a), in line with the antiepileptic effectiveness of vagal stimulation (Amar 2007), the involvement of mirror neurons and dopaminergic activation (Liao et al. 2015, Lin et al. 2010, Lin & Yang 2015). Nevertheless, music is a powerful agent of neuroplasticity capable of altering connections between neuronal networks and inducing brain reorganization (Wan & Schlaug 2010). This inherent power of music may justify its potential therapeutic as well as harmful effect in epilepsy and other neuropsychiatric disorders.

In conclusion, our study provides further contribution supporting the recommendation of listening to music as an add-on treatment in the clinical management of epilepsy; this is particularly valuable in the case of drug-resistant epilepsy, where standard pharmacological treatments have not proven to be effective.

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Conflict of interest: *None to declare.*

Contribution of individual authors:

Patrizia D'Alessandro: study conception and preparation, interpretation of data, drafting manuscript;

Marta Giuglietti, Antonella Baglioni: trial execution, acquisition of data;

Norma Verdolini: achievement of the approval of the Ethics Committee;

Nicola Murgia: statistical analysis; Massimo Piccirilli, Sandro Elisei: study preparation, interpretation of data, revising manuscript.

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