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Mozart's music in children with drug-refractory epileptic encephalopathies: Comparison of two protocols

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ABSTRACT

In this prospective, randomized, open label study, we compared the effect on seizure recurrence and quality-of-life parameters, of two different protocols of music therapy in children and adolescents with refractory epileptic encephalopathies. Nine out of 19 patients (13 males and 6 females, aged between 1 and 24 years) were randomized to listen to Mozart's sonata in D major for two pianos K448 for 2 h/day for 2 weeks; other 10 children were randomized on a set of Mozart's compositions.
In group 1 (K448), 2/9 children (22.2%) had a ≥75% seizure decrease; two patients had less than 50% seizure reduction, and the other five were unchanged.
In group 2 (set Mozart), 7/10 patients (70%) had a significant seizure reduction (specifically, ≥50% in 1/10; ≥75% in 4/10; 100% in 2/10).
An overall more significant behavioral improvement including less irritability and tearfulness, reduced self-/heteroaggression, a better daytime vigilance, and nighttime sleep quality, was also reported in children from group 2.
In conclusion, the present study seems to confirm that music therapy may be an additional, nonpharmacological, effective treatment for patients with refractory epileptic seizures in childhood. The Mozart's set of different compositions can be better accepted and effective than the K448.

1. Introduction

In recent years, musical stimulation, in particular the "Mozart effect" of the K448 sonata for two pianos, has been reported to decrease both interictal electroencephalographic (EEG) discharges [1–3] and recurrence of clinical seizures [4–8]. More recently, a set of Mozart's compositions was reported to be particularly beneficial in reducing seizure recurrence in children and adolescents with drug-resistant structural or genetic epileptic encephalopathies. Improved nocturnal sleep quality together with positive behavioral and mood changes were also reported. Furthermore, children appeared more compliant to a set of different music proposals than a single composition like Mozart's K448 [9]. Nevertheless, in so far available studies, there is a significant diversity with respect to protocols of music therapy as well as for kind of musical compositions, length of daily music listening, and duration of follow-up. Therefore, we conducted a prospective, randomized, open label study comparing two different protocols. Following Tomatis' method [10], Mozart's K448 sonata or Mozart's set of compositions were compared on their effect on seizure recurrence and quality-of-life parameters, including nocturnal sleep and mood/behavioral changes, in children and adolescents with refractory epileptic encephalopathies [9].

2. Materials and methods

Patients were recruited from the center for children and adolescent epilepsy care of the Medical School of the University of Salerno. The protocol was approved by the Ethics Committee, and the study was not sponsored by any commercial organization. They were selected according to the following criteria: (i) 12 or more months of age; (ii) with seizures refractory to antiepileptic drugs; (iii) with drug-resistant epilepsy and with at least four seizures a week during the 6 months before music therapy was administered; (iv) without systemic or progressive neurologic diseases (including deafness); and (v) with informed consent by parents and/or caregivers to participate in the study. Exclusion criterion was poor compliance with following the study protocol. Nonepileptic

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seizures were excluded through video-EEGs and/or long-term monitoring EEGs. Brain computed tomography/magnetic resonance imaging scans were performed in all cases. Seizure frequency, type, and duration were recorded by parents and caregivers, both at home and at school, in an epilepsy diary. Seizures were classified according to the International League Against Epilepsy (ILAE) classification of epileptic seizures [11]. The effectiveness of music therapy was rated as follows: seizure-free (100% remission); very good (50–98% decrease in seizure frequency); minimal (seizure frequency less than 50% with minimal change in seizure severity); and unmodified or worsened (seizure frequency and severity similar to [unmodified] or worse than [worsened] baseline).

Before starting the treatment (TIME 0), parents/caregivers of each patient were administered a questionnaire, designed to assess the following variables: seizure frequency and type, quality of nocturnal sleep, daytime mood and behavior (irritability, fits of rage, crying spells, self-/heteroaggression), and gastrointestinal function (i.e., constipation, abdominal pain attacks), throughout the 6 months prior to treatment onset. Laboratory assessment including antiepileptic drug blood level, full blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), urea, creatinine, ammonium, and urinalysis, together with a sleep–wake video-EEG recording, was performed in each patient in the previous week.

Soon after, each child was delivered with a device (see later), and his/her parents/caregivers had an exhaustive training for home treatment. Parents were also provided a website password where they could daily connect in order to download the selected music. Compliance to protocol was thus monitored. Moreover, parents were asked to report the type, duration, and frequency of the seizures in a diary, as well as changes in their child's daily activities and/or behavior and self-deemed compliance to protocol.

Patients randomized to group 1 were asked to listen to Mozart's sonata in D major for two pianos, K448, 2 h a day for 15 days (total number of hours = 30). Children could listen to the music anytime during the day, even during sleep.

The same schedule (2 h a day, for 15 days, 30 h in total) was applied to patients randomized to group 2, who had to listen a set of Mozart's compositions including: symphony No. 41, K551; piano concerto No. 22, K482; violin concerto No. 1, K207; violin concerto No. 4 in D major, K218, allegro aperto; symphony No. 46 in C major, KV96, allegro; and flute concerto in D major K314, allegro aperto.

Both groups listened to the music modified by an electronic device called “electronic ear” [10]. The latter, through a system of filters, amplifiers, and sophisticated mechanisms of electronic gate, modifies the amplitude of sound frequencies preferably delivering higher sound frequencies (N3000 Hz) which, according to Tomatis, “recharge” the cerebral cortex. The electronic ear works on the middle ear through the contraction of the muscles of the hammer and the bracket. The sound is transmitted through both air conduction and bone conduction. Through the air, the sound signal reaches the eardrum, whose active vibration stimulates the cochlea in the inner ear. Through bone conduction, the sound message is transmitted directly on the skull from a vibrator placed on the top of the cap. The sound, in this way, directly reaches the inner ear, bypassing the eardrum.

Fifteen days later, patients were clinically reassessed, antiepileptic drug dosages were evaluated, the music device and the filled-in diary regarding the first 15 days of treatment were retrieved.

No changes to the antiepileptic treatment or addition of other drugs, except rescue drugs, were allowed throughout the study.

Statistical analyses were performed by means of SPSS (SPSS Inc., USA, 2006). Data are expressed as mean ± standard deviation (SD). Two-way analysis of variance (ANOVA) was carried out to compare the number of seizure attacks before and after listening to Mozart's K448 or Mozart set of compositions. The *t*-test was used to compare the percentage reduction in seizure frequency between the two groups. A P-value less than 0.05 was set as significant.

3. Results

According to the inclusion criteria, 19 children (13 males and 6 females) were recruited, aged between 1 and 24 years at the beginning of the administration of music therapy with a mean age of 14.2 years (group 1) and 12.1 years (group 2). All patients were suffering from drug-resistant epileptic encephalopathies or syndromes.

Diagnoses were as follows: multifocal encephalopathy with spasms and tonic seizures (n = 16); Lennox–Gastaut syndrome (n = 2); and secondarily generalized cryptogenic partial epilepsy (n = 1). All patients but one (18/19) had a severe/profound degree of intellectual disability associated, in 13 out of 18, with a severe type of cerebral palsy (spastic quadriplegia with or without dystonia, n = 11; double hemiparesis, n = 1; right hemiplegia, n = 1). One patient had a mild intellectual disability.

The mean number of the antiepileptic drugs was 3.3 (group 1) and 3.2 (group 2), combined with the ketogenic diet in 4 children.

Seizure recurrence before music therapy was more than 1/day in 16/19 patients, more than 1/week in 3/19.

Nine out of 19 patients were randomized to listen to Mozart's sonata in D major for two pianos K448 for 2 h/day for 2 weeks; the other 10 children were randomized on a set of Mozart's compositions (including No. 41, K551 symphony; piano concerto No. 22, K482; Violin Concerto No. 1, K207; Violin Concerto No. 4 in D major, K218, cheerful open; Symphony No. 46 in C major, KV96, cheerful; Flute Concerto in D major K314, cheerful open) for 2 h a day for 15 days.

The clinical characteristics of patients randomized to receive the K448 or Mozart set are summarized in Table 1.

In group 1 (K448), 2/9 children (22.2%) had a >75% seizure decrease, two patient had less than 50% seizure reduction, and the other five were unchanged. In this group, parents reported a decreased irritability and tearfulness in 2 children, and a better gastrointestinal functioning in another one.

In group 2 (set Mozart), 7/10 patients (70%) had a significant seizure reduction (specifically, >50% in 1/10; >75% in 4/10; 100% in 2/10) (Fig. 1).

With respect to behavioral effects, parents reported decreased irritability and tearfulness in 8 patients, increased daytime activity in 7, improved sleep habits (decreased time to fall asleep reduction in night,

Table 1
Characteristics of patients of group 1 (K448) and group 2 (set Mozart).

	Group 1 (9 pts)	Group 2 (10 pts)
Sex	5 males; 4 females	8 males, 2 females
Age (years) mean, range	14.2 (1–24)	12.1 (1–23)
Mental delay		
Mild	1	–
Moderate	–	–
Severe	5	4
Profound	3	6
Cerebral palsy		
Spastic tetraplegia	7	8
Double hemiplegia	–	1
Spastic dyskinetic	–	1
Hemiplegia	1	–
Epilepsy type		
Epileptic encephalopathy	6	10
LGS	2	–
Focal epilepsy ± SG	1	–
Seizure type		
Spasm	2	1
Tonic	5	4
Atypical absences	3	1
Clonic	–	1
Focal ± SG	2	3
Seizure frequency		
≥1/day	6	5
≥1/week	3	5
Number of AEDs (mean, range)	3.3 (2–4)	3.2 (2–4)

Legend: LGS, Lennox–Gastaut syndrome; SG, secondary generalization; AED, antiepileptic drug.