



## Mozart's music in children with drug-refractory epileptic encephalopathies



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### ABSTRACT

Mozart's sonata for two pianos in D major, K448, has been shown to decrease interictal EEG discharges and recurrence of clinical seizures in both adults and young patients. In this prospective, open-label study, we evaluated the effect of listening to a set of Mozart's compositions, according to the Tomatis method, on sleep quality and behavioral disorders, including auto-/hetero-aggression, irritability, and hyperactivity, in a group of children and adolescents with drug-resistant epilepsy.

The study group was composed of 11 outpatients (7 males and 4 females), between 1.5 years and 21 years of age (mean age: 11.9 years), all suffering from drug-resistant epileptic encephalopathy ( $n = 11$ ). All of them had a severe/profound intellectual disability associated with cerebral palsy. During the study period, each patient had to listen to a set of Mozart's compositions 2 h per day for fifteen days for a total of 30 h, which could be distributed over the day depending on the habits and compliance of each patient.

The music was filtered by a device preferably delivering higher sound frequencies ( $>3000$  Hz) according to the Tomatis principles. The antiepileptic drug therapy remained unchanged throughout the study period. During the 15-day music therapy, 2 out of 11 patients had a reduction of 50–75% in seizure recurrence, and 3 out of 12 patients had a reduction of 75–89%. Overall, 5 (45.4%) out of 11 patients had a  $\geq 50\%$  reduction in the total number of seizures, while the percentage decrease of the total seizure number (11/11) compared with baseline was  $-51.5\%$  during the 15-day music therapy and  $-20.7\%$  in the two weeks after the end of treatment. All responders also had an improvement in nighttime sleep and daytime behavior.

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## 1. Introduction

Among the so-called alternative nonpharmacological treatments for drug-resistant epilepsy, in addition to surgery, vagus nerve stimulation, ketogenic diet, and deep brain stimulation, there is a growing interest in music therapy.

In fact, there are a few studies reporting that the musical stimulation, particularly the “Mozart effect” of the K448 sonata for two pianos, is able to decrease both interictal EEG discharges [1–3] and recurrence of clinical seizures [4–8].

As to the interictal discharges, there is some evidence for the particular responsiveness of generalized and central spike-and-wave discharges to music therapy [3], with an effect that persists even after discontinuing music stimulation (“carryover effect” according to Lin et al. [2]).

With respect to clinical seizures, there is only a randomized controlled trial [8] in adults with epilepsy and neurological disorders, and

there are a few other small studies in children and adolescents with several forms of epilepsy (particularly idiopathic), with protocols differing for duration and kind of musical stimulation (especially Mozart K448 for 2 pianos) and length of follow-up [3,4,8,9].

In this prospective, open-label trial, we evaluated the effect of listening to a set of Mozart's compositions, according to the Tomatis method [10], on seizure recurrence, sleep quality, and behavioral disorders, including auto-/hetero-aggression, irritability, and hyperactivity, in a group of children and adolescents with drug-resistant epileptic encephalopathies.

## 2. Materials and methods

The patients were recruited from the center for children and adolescent epilepsy care of the Medical School of the University of Salerno.

They were selected according to the following criteria: (i) 12 months of age and over; (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

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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.

The protocol was approved by the Ethics Committee, and the study was not sponsored by any commercial organization.

Nonepileptic seizures were excluded by means of 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), each patient was administered a questionnaire, designed to evaluate seizure frequency and type, quality of nocturnal sleep, and daytime behavior (irritability, fits of rage, crying spells, self-/hetero-aggression) throughout the 6 months prior to treatment onset. Laboratory evaluation including antiepileptic drug blood level, a full blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), urea, creatinine, and urinalysis, together with a sleep–wake video-EEG recording, was performed in each patient in the previous week.

On the same day, a wake video-EEG recording before, during, and after listening to the music of the same duration (20 min, respectively) was performed in each patient.

Soon after, each child was delivered with a device, and his/her parents/caregivers had an exhaustive training for home treatment.

Parents were also given an epilepsy diary in which they had to record seizure number, type, and duration both at home and at school as well as changes in the quality of nocturnal sleep and daytime behavior.

The set of music to be administered included Mozart's compositions (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; flute concerto in D major K314, allegro aperto).

Mozart's compositions were modified by a device, the so-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 (>3000 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.

The music had to be listened to 2 h per day for fifteen days for a total of 30 h and listening time could be distributed over the day depending on the habits and compliance of each patient. At study entry, parents were given a password to access a dedicated website and listen to Mozart's compositions. In this way, full compliance with the study protocol could be monitored. If daily music listening was irregular or insufficient, a given patient would be excluded from the study.

After 15 days (TIME 1), each patient underwent a second wake video-EEG recording lasting 20 min. The music device and the filled-in diary regarding the first 15 days of treatment were retrieved, and a blood sample for antiepileptic drug level evaluation was taken. Parents were then given a new diary to record seizure recurrence and type together with nocturnal sleep quality and behavioral changes during the next month in the absence of music stimulation.

After 1 month (TIME 2), a wake video-EEG recording was then performed on each patient. Throughout the study, no changes to the anti-epileptic treatment or addition of other drugs, except rescue drugs, were allowed.

Statistical analysis was performed by means of SPSS (SPSS Inc., USA, 2006). Data are expressed as mean  $\pm$  SD. The paired *t*-test was used to compare the percentage reduction in seizure frequency throughout the music therapy with the premusic seizure frequency set at 100%. Analysis of variance two-way analysis of variance was carried out to compare percentage seizure frequency reduction after listening to Mozart's set of compositions with respect to sex, etiology, IQ, and seizure type. A *p*-value less than 0.05 was set as significant.

### 3. Results

The study group was composed of 11 outpatients (7 males and 4 females), between 1.5 years and 21 years of age (mean age: 11.9 years), all suffering from drug-resistant epileptic encephalopathy ( $n = 11$ ).

All patients (11/11) had a severe/profound intellectual disability associated with cerebral palsy (spastic tetraparesis with or without dystonia,  $n = 9$ ; double hemiparesis,  $n = 1$ ; right hemiparesis,  $n = 1$ ).

The clinical EEG and neuroradiological features of each patient are summarized in Table 1.

The mean number of the antiepileptic drugs was 3.4; two patients were also on a ketogenic diet.

Seizure recurrence relative to all patients before, during, and after music therapy is shown in Fig. 1. During the 15-day music therapy, 2 out of 11 patients had a reduction of 50–75% in seizure recurrence, and 3 out of 12 patients had a reduction of 75–89%. None of the patients were seizure-free. The remaining patients showed minimal or no changes in seizure frequency (a decrease of 25–49% in 2, less than 25% in 2, and unchanged in the other 2). Overall, 5 (45.4%) out of 11 patients had a  $\geq 50\%$  reduction in the total number of seizures, while the percentage decrease of the total seizure number (11/11) compared with baseline was  $-51.5\%$  during the 15-day music therapy and  $-20.7\%$  in the two weeks after the end of treatment. The average percentage seizure reduction for all patients at the end of music treatment compared with the premusic seizure frequency was  $48.4 \pm 48.7\%$  ( $CI = 56 \pm T(10) * 21.18662$ ,  $p = 0.02$ ; Student's *t*-test). No statistically significant difference was observed between patients with different severities in IQ ( $p = .111$ ), etiology ( $p = .109$ ), gender ( $p = .107$ ), and seizure type ( $p = .107$ ).

With respect to the relationship between the response to music therapy and the localization of spike-and-wave discharges, occipital/bioccipital discharges were present in 20% of the responders and in 66.7% of the nonresponders (Fig. 2).

Nighttime sleep was improved (easier falling asleep and less early morning awakenings) in 4 (36.4%) out of 11 patients; all were included among responders. One of the responders, however, had a regular sleep before treatment.

According to their relatives, all responders also presented a behavioral improvement, i.e., being more quiet and attentive to the environmental stimuli. Treatment compliance was generally good both in children and in parents.

### 4. Discussion

In this short-term prospective study, music therapy, consisting of a set of Mozart's compositions administered according to the principles of the Tomatis method, was associated with a significant reduction in seizure recurrence and an improved daytime behavior and quality of nighttime sleep in about 45% of children and adolescents with drug-resistant epileptic encephalopathies associated with psychomotor developmental delay/intellectual disability.

Currently, there are a few reports on the effect of music listening on interictal epileptic discharges [1–3] and seizure recurrence [4–8].

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