Editorial

Mozart's music in children with epilepsy

Lung-Chang Lin[1,2], Rei-Cheng Yang[2,3]

[1]Department of Pediatrics, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Department of Pediatrics, Changhua Christian Hospital, Changhua, Taiwan

Correspondence to: Rei-Cheng Yang, MD, PhD. Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, #100, Tzu-you 1st Road, Kaohsiung 80708, Taiwan. Email: rechya@kmu.edu.tw.

Abstract: Coppola *et al*. reported 5 out of 11 patients suffering from drug-resistant epileptic encephalopathy associated with cerebral palsy had a ≥50% reduction in the total number of seizures after listening a set of Mozart's compositions 2 h per day for 15 days. Our previous studies also revealed that both seizure frequencies, recurrence of first unprovoked seizure, and epileptiform discharges are significant reduced after listening to Mozart K.448. Until now, the real mechanism of music effect on epilepsy is still unclear. In this article, in addition to showing the beneficial effects of music on seizure, and epileptiform discharges, we are going to discuss the possible mechanism of music. The possible mechanisms include dopaminergic pathways, mirror neurons, and parasympathetic activation after listening to music.

Keywords: Mozart K.448; epilepsy; epileptiform discharges; children

Submitted Sep 14, 2015. Accepted for publication Sep 17, 2015.
doi: 10.3978/j.issn.2224-4336.2015.09.02
View this article at: http://dx.doi.org/10.3978/j.issn.2224-4336.2015.09.02

We carefully reviewed the article entitled with "Mozart's music in children with drug-refractory epileptic encephalopathies". The results show that after listening a set of Mozart's compositions 2 h per day for fifteen days, over 50% of seizure reductions compared with baseline are observed in 5 out of 11 patients with epileptic encephalopathy. Hughes *et al*., first report music effect on epilepsy when they found reductions in epileptiform activities in comatose patients, with status epilepticus or with periodic lateralized epileptiform discharges (PLEDs) during exposure to Mozart K.448 (1). Emerging evidence continues to demonstrate the positive effects of music on epilepsy, and in some case, the use of Mozart's music, in particular. Our previous study also showed similar effects with Coppola's results. Over 70% of children with refractory epilepsy had a ≥50% reduction in seizure frequencies after at least 6 months of Mozart K.448 listening once per night (2).

Hughes *et al*. found that the epileptiform discharges decrease during listening to Mozart K.448 in 23 of 29 patients with epilepsy (1). Our previous study also showed that epileptiform discharges in patients with epilepsy are significantly decreased during and right after listening to Mozart K.448. The largest reduction in discharges is observed among patients with generalized or central epileptiform discharges (3). In another study, Turner reports that interictal epileptiform discharges decrease in four subjects with rolandic seizure when they are listening to Mozart K.448 (4). In addition to human studies, Mozart music also showed beneficial effect in Long Evans rats with spontaneous absence seizure. In our previous study, seizure frequencies and spontaneous discharges were reduced in all of the spontaneous absence epilepsy rats during and after music exposure compared with the pre-music stage (5).

Our previous study demonstrated eighteen children with epilepsy who were clinically well-controlled by antiepileptic drugs were enrolled for the evaluation the long-term effect on epileptiform discharges (6). Each of the children had electroencephalograms (EEG) that revealed persistent epileptiform discharges for at least 6 months. There were no significant changes in epileptiform discharges after more than 6 months of AED treatment prior to music exposure. However, significant decreases in epileptiform discharges were found after 1, 2, and 6 months of listening to Mozart K.448 when compared with EEGs before listening to music (6).

Refractory childhood epilepsy accounts for 20-30% of cases of epilepsy (7). In addition to epileptiform discharges, we used the Mozart K.448 in the children with refractory epilepsy (2). The number of seizures was compared before and after listening to Mozart K.448. The effectiveness of music therapy was rated as: (I) (seizure free) 100% remission; (II) (very good) a decrease in seizure frequency by 50-98%; (III) (minimal) seizure frequency less than 50% with minimal change in seizure severity; and (IV) unmodified or worsened when seizure frequency and severity were found to be the same as (unmodified) or worse than baseline (worsened), respectively (8). The results demonstrated eight of eleven patients were seizure free (n=2) or had very good responses (n=6) after 6 months of listening to Mozart K.448. In a case report, improvement of seizure control in a 56-year-old gentleman who had refractory gelastic epilepsy was also found by Lahiri *et al*. (9). The patient listened to non-specific piece of Mozart's music 45 min daily. In the 3 months during which he had listened to Mozart, he did not have any secondarily generalized tonic-clonic seizures. Accordingly, Mozart music could be used as a potential add-on therapy in the treatment of patients with refractory epilepsy.

As we know, Mozart K.448 is not the only piece of music to have beneficial effects on children with epilepsy. Other music with lower harmonics may also decrease epileptiform discharges in epileptic children (10). There are a variety of components in virtually every kind of music, including a melody, rhythm, tone, and harmony. Each of these musical elements may play an important role in the beneficial effects of music. To analyze the periodicity of music, Hughes *et al*. first converted musical notes into audio waveforms, i.e., acoustical pressure waves converted to voltage signals and digitized. A periodicity index was chosen to represent the degree of periodicity; this index was the ratio of the highest peak to the next highest (×10) (11). Hughes *et al*. found that the long-term periodicity of melodic line in the music of Mozart and two pieces of Bach's were significantly more apparent and frequent when compared with the music of 55 other composers (such as Chopin, Mendelssohn) (11). This may account for the reduction of epileptiform discharges. In another study, Zhao *et al*. report that both happy and sad melodies of equal valence resulted in significant lower pain scores during pain test and were in contrast to the mood prediction. It indicates that the valence of music, rather than the mood it induced, appears to be a critical factor of the hypoalgestic effect of music (12). In our previous study, interictal discharges were reduced by an average of 24.1% in 81% of patients as patients listened to the Mozart K.448. However, when we used a digitally computerized string version of the same musical stimulus, the discharges showed slight increase by average 10.5% when listening to this music (3). A spectrogram analysis of the two versions, piano and string, was generated by a MATLAB program (Mathworks, Inc., MI, USA). To begin to describe the differences in the two versions, short-time Fourier transforms of the signals were computed. Although the two kinds of music had the same melody, spectrograms comparing the piano K.448 and string K.448 showed clear differences. The differences were particularly noteworthy at high frequencies. The string K.448 had much stronger high frequency harmonics. The piano K.448 seemed to concentrate more energy in the fundamental frequency and the lower harmonics (3). On the other hand, we use the Mozart K.545 which shares similar spectrogrammatic characteristic with Mozart K.448 to investigate the effect of harmonics on epileptiform discharges in epileptic children. There was a significant decrease in the frequency of epileptiform discharges during and right after listening to Mozart K.448 and K.545 (10). We suggest that Mozart K.448 is not the only piece of music to have beneficial effects on children with epilepsy, and that listening to Mozart K.545 with similar lower harmonics can decrease epileptiform discharges in epileptic children as well.

Recently, several theories have been introduced regarding the effects of sound on the brain. Neurotransmitter pathways may be involved in the effect of Mozart's music on epilepsy. Musical exposure is known to increase the expression of dopamine levels in the brain (13). In recent years, there are numbers of evidence implicating a role for dopamine in the pathophysiology of epilepsy. A Positron Emission Tomography study showed that the impaired dopamine uptake in the midbrain is hypothesized to contribute to seizures in juvenile myoclonic epilepsy (14). In a recent animal study, the authors report that pentylenetetrazole-induced seizures decreased the dopamine levels in striatal and hippocampal areas, accompanying the induction and propagation of seizures (15). It is possible that listening to music modifies the dopaminergic pathways contributing to the beneficial effects in epilepsy therapy.

Another theory is that a 'Mozart effect' might be mediated through sensory-motor circuits by so-called mirror neurons. Mirror neurons are proposed to be a particular type of neurons that are modified when an individual performs an action and is exposed to visual/music stimulation (16,17). The link between music and motor

function is evident in some aspects of musical activity. For example, we dance to music, we move our bodies to play musical instruments, and we move our mouths and larynges to sing (17). A recent neuroimaging study examining transcranial magnetic stimulation and behavior suggests that auditory stimulation can modulate the activity of the motor system (18). Although there is no direct evidence to support this hypothesis, it is possible that mirror neurons mediate neuron activity by linking auditory stimulation directly to the motor cortex (19).

Heart rate variability (HRV) analysis has been used extensively in the analysis of autonomic function (20). In a meta-analysis study, patients with epilepsy showed lower vagal and higher sympathetic tone when compared to controls (21). Mukherjee *et al*. reported that higher sympathetic tone, lower parasympathetic tone, and more severe dysautonomia were found in patients with intractable epilepsy than in those with well-controlled epilepsy (22). Another study demonstrated that parasympathetic activity was found to be decreased high-frequency (HF), increased low-frequency (LF)/HF ratio of HRV analysis in patients with epilepsy without antiepileptic drug therapy when compared to patients with antiepileptic drug therapy (23). According to these findings, an increase in parasympathetic activity may help to improve seizure control. In our recent study, we also found that listening to Mozart music decreased epileptiform discharges and significantly increased HF, the square root of the mean squared differences of successive RR intervals (RMSSD), and the standard deviation of differences between adjacent RR intervals (SDSD) (24). Most of the patients of effective outcome showed a decreased LF/HF ratio, LF normalized units (LF nu), mean beats per minute (bpm) and an increased HF normalized units (HF nu), which all indicated parasympathetic activations (24). In addition to our study, one study demonstrated that a 2-hour music intervention by listening and singing Taiwanese popular songs in cancer patients increased their relaxation scores and parasympathetic activities (25). These results mentioned above all indicate that parasympathetic tone increased during music exposure, which may in part account for the reduction of epileptiform discharges in epilepsy.

Conclusions

There is evidence that listening to Mozart's music, short-term and long-term, may contribute to decreases in epileptiform discharge and seizure frequency in children with epilepsy, even in refractory type. Not being identical for Mozart K.448, music with lower harmonics, such as K545, might decrease epileptiform discharges in epileptic children. Although some studies reported the possible mechanisms responsible for the beneficial effects of music in patients with epilepsy, the real mechanism is still unclear. More studies are necessary to clarify the music effects on the brain regions, which make the music more applicable in clinical settings.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Lin LC, Yang RC. Mozart's music in children with epilepsy. Translational Pediatrics 2015;4(4):323-326. doi: 10.3978/j.issn.2224-4336.2015.09.02

