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Perampanel for nonepileptic myoclonus in Angelman syndrome

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Abstract

Background: Angelman syndrome (AS) is a neurodegenerative disorder caused by functional loss of the maternal ubiquitin-protein ligase 3A gene. Nonepileptic myoclonus, also described as tremulous movement, often occurs during puberty and increases in adulthood. The involuntary movement in AS has not been defined patho-physiologically and the drugs used such as levetiracetam and piracetam *are not always* effective. Recently, the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonist, perampanel (PER), was used to alleviate myoclonus in progressive myoclonus epilepsy. Herein, we tested the efficacy of PER for nonepileptic myoclonus.

Methods and results: Four patients with AS, aged from 20 to 40 years at the beginning of treatment, were enrolled in our study. All patients reported disruption to their daily lives from the myoclonus movement. They experienced mild to moderate improvement with the starting dose of 2 mg. The dose was increased to 4 mg in one patient to achieve sufficient efficacy, while two had their dose reduced to 1 mg due to dizziness or possible exacerbation of myoclonus. The last patient continued to take the starting dose. Follow-up over 16 to 20 months revealed a significant reduction in the severity of nonepileptic myoclonus in all patients.

Conclusion: Our study suggests that PER could be one of the promising drugs for nonepileptic myoclonus in AS.

Key words: Angelman syndrome, perampanel, myoclonus, involuntary movement

1. Introduction

Angelman syndrome (AS) is a neurodegenerative disorder caused by a functional loss of maternal ubiquitin-protein ligase 3A gene (*UBE3A*). After the first cases of AS were reported in 1965, the molecular basis and the clinical features have been gradually revealed, including recent studies on the clinical features in adolescence and adulthood [1-3]. Among them, erratic myoclonus-like involuntary movement is a prominent feature that disturbs the daily lives of affected patients; it often presents during puberty and gets worse in adulthood. The etiology and patho-physiology of myoclonus in patients with AS remains controversial. Guerrini et al. subsequently showed that 5-10 Hz rhythmic activities preceded the myoclonus and described the myoclonus as fast-bursting cortical myoclonus [4]. But sometimes electroencephalography monitoring cannot detect an accompanying epileptic discharge. Myoclonic seizures are also common in AS, but are easy to distinguish by the following features [5]: short duration and onset in young childhood. In contrast, episodes of nonepileptic myoclonus last from seconds to hours and have a much later onset, beginning in either adolescence or early adulthood. Individuals with AS may also develop myoclonic status epilepticus, although the long-lasting episodes of nonepileptic myoclonus are associated with no significant alteration of consciousness, no regression of skills, and no postictal period. Nonepileptic myoclonus usually begins in the hands and spreads to the upper and/or lower extremities and, occasionally, the face. Although drugs such as piracetam (PIR), levetiracetam (LEV), and benzodiazepines are used for treatment, they are not always effective [2,4].

Perampanel (PER) is a novel antiepileptic drug that selectively inhibits the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)-type ionotropic glutamate receptor. PER is prescribed as adjunctive therapy for focal epilepsies and primary generalized tonic-clonic seizures, and recently, it showed efficacy for myoclonic seizures and for myoclonus such as in progressive myoclonus epilepsy (PME) [6-8].

Herein we sought to test the efficacy of PER for nonepileptic myoclonus in four patients with AS.

2. Materials and Methods

Four patients with AS were enrolled into our study from those regularly followed in Hokkaido University Hospital (Table 1). All of them had microdeletion of maternal 15.q11.2-13.1, the most common molecular subtype of AS. We administered PER for nonepileptic myoclonus during the period from May 2017 to July 2017, starting with a dose of 2 mg and reducing or escalating the amount according to the efficacy and side effects.

Patients were followed for 16 to 20 months and the effect of PER was assessed at the latest follow-up.

The reduction rate was calculated by the following formula: (duration of myoclonus before administration of PER) x (number of days that myoclonus occurred before administration of PER) / (duration of myoclonus after administration of PER) x (number of days that myoclonus occurred after administration of PER).

All procedures used in this research were approved by the Ethical Committee of Hokkaido University Hospital. All patients or parents provided written informed consent.

3. Case reports

Patient 1 was a male with past history of epilepsy. He had generalized tonic-clonic seizures since he was two years old that were treated with sodium valproate (VPA). The convulsions disappeared for years, but atypical absence seizures remained, and he continued taking VPA. Around the age of 26 years, nonepileptic myoclonus appeared and worsened with age; it affected his ability to fall asleep and to feed himself. The myoclonus was described as continuous jerking with decreasing and increasing severity

which was sustained for about 15 hours. The jerking stopped during sleep. It occurred once or twice a week. PIR was initiated at the age of 38 years, but achieved only a partial effect, and he was subsequently treated with PER (2 mg dose) at the age of 42 years. His myoclonus immediately shortened to about 5 hours, so we increased the dose to 4 mg, which stopped the myoclonus before sleep disappeared and he was able to stop PIR. At the last visit, he had myoclonus for about 5 hours once or twice a week, which means a 66% reduction.

Patient 2 was a female with past history of epilepsy. She had the first generalized tonic-clonic seizure at the age of 12 years. She also had focal impaired awareness seizures and was treated by VPA and clonazepam (CZP). At 15 years of age, a nonepileptic myoclonus of continuous jerking with decreasing and increasing severity emerged, but with no convulsions present, she was initially treated with alternating VPA and LEV for the myoclonus. After no change in the symptoms, PIR was introduced, also unsuccessfully. Her myoclonus gradually worsened in duration and severity with age, and PER was administered at the age of 27 years, when she had erratic myoclonus mainly on her right face and right upper extremities lasting for 5 to 10 minutes, 10 to 20 times a day. The starting dose of 2 mg was escalated to 4 mg two months later because it produced insufficient efficacy. Soon after the dose increase, she developed dizziness and stopped PER by her own volition. Her myoclonus recurred thus PER was reintroduced at the dose of 1 mg and her myoclonus decreased to 3 to 5 times a month for 30 minutes each. Her myoclonus was exaggerated temporarily when her intake of PER was accidentally stopped for a month. At the last visit, she took 3 mg of PER and she had myoclonus 2 to 3 times a month for 20 to 30 minutes each (Fig.1), which means a 99% reduction.

Patient 3 was a female with past history of epilepsy. When she was 2 years old, she had multiple generalized tonic-clonic seizures and started VPA. She also had focal impaired awareness seizures thus clobazam (CLB) was added to the treatment.

Nonepileptic myoclonus of erratic tremulous movement of her upper extremities almost every morning that disturbed her during sleep, appeared around 9 years of age and gradually started to affect her daily life. At the age of 23 years, she started to take 2 mg of PER. She showed transient exacerbation of the involuntary movement and the dose was reduced to 0.5 mg, which subsequently seemed to be ineffective, and the dose was increased to 1.2 mg. Her myoclonus decreased from 30 minutes every morning to 2 to 3 times a week for 10 to 15 minutes each by the last visit, which means an 85% reduction.

Patient 4 was a male with past history of epilepsy. He had generalized tonic-clonic seizures and atonic seizures. He was prescribed VPA and CZP, and the last convulsion was at the age of 14 years. Approximately 2 years later, a nonepileptic myoclonus of tremulous movement predominantly of his lower extremities, but sometimes of his upper extremities, appeared monthly, often lasting for hours. PIR was scarcely effective, so he started to take PER at the age of 31 years. The initial dose of 2 mg was effective in reducing the symptom frequency and duration, and his myoclonus disappeared when the dose was escalated to 4 mg.

All patients had a clear clinical response in their nonepileptic myoclonus with a minimal dose of PER (Table 1). Although all the patients retained some level of involuntary movement at their last visits, all the patients and/or caregivers were satisfactory with the result. One patient experienced dizziness as a side effect, but it disappeared with a dose reduction.

We could not undertake neurophysiological examination such as video-surface electromyography-electroencephalography recordings and short-latency sensory evoked potentials (SEPs), because all patients had severe intellectual deficits and could not stay in the laboratory for testing.

4. Discussion

Cortical myoclonus is usually treated with one of several agents including LEV,

PIR, VPA, CZP, and zonisamide [9]. In AS, the choice of treatment for myoclonus is the same and the most commonly prescribed medications are LEV, CZP, and CLB [2]; however, none of these medications show high rates of efficacy [5].

Recently PER proved effective for myoclonus in PME such as in Lafora disease, Unverricht-Lundborg disease, and dentatorubral-pallidoluysian atrophy [6,8,10]. Canafoglia *et al.* recently reported the efficacy of PER for patients with PME [11]. They evaluated the efficacy of PER using the minimal myoclonus scale and the Unified Myoclonus Rating Scale. They showed significant improvement in the minimal myoclonus scale and “patient questionnaire”, “myoclonus with action”, “myoclonus at rest”, “stimulus sensitivity”, “negative myoclonus” and “functional tests” in the Unified Myoclonus Rating Scale. Furthermore, Oi *et al.* recently demonstrated the efficacy of PER for refractory cortical myoclonus with a low-dose regimen [12]. They showed dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex using early components of SEPs. They showed dose-dependent prolongation of latency of P2 and N33 components. They also demonstrated that giant SEPs before treatment decreased in amplitude and the latency was prolonged by PER. They suggested that PER might lessen the degree of synchronized discharges in the postsynaptic neurons in the primary motor cortex. There have only been a few reports evaluating SEPs in AS, and Guerrini *et al.* mentioned a lack of giant SEPs in AS patients [4]. They subsequently assessed the correlation between the concentration of PER and activities of daily life and demonstrated a favorable evaluation in patients who took low-dose PER. In our present case series PER was also effective for myoclonus-like movement in AS, and as for the other conditions, it was effective in a small dose of 1 or 2 mg. Unfortunately, we cannot elucidate how PER works to reduce the involuntary movement in AS because the pathophysiology underlying why nonepileptic myoclonus occurs frequently in patients with AS remains unclear.

Regarding side effects, patient 2 had dizziness with 4 mg of PER, but it

disappeared with a dose decrease to 1 mg. Patient 3 seemed to show exacerbation of myoclonus with 4 mg of PER, but later its efficacy was apparent. Other possible side effects such as weight gain or psychological and behavioral problems were not apparent in the present patients.

5. Conclusions

In this small case study, PER was effective for reducing nonepileptic myoclonus in all patients, and a dosage as low as 1 mg/day might achieve a sufficient effect for patients and their caregivers. It should be noted that dizziness can still occur with a low dose and patients should be monitored closely. This is a preliminary study and larger prospective studies should be done to clarify the efficacy, optimal dose, and long-term effect of PER for AS.

6. Conflict of interest

The authors have no conflicts of interest to disclose.

7. Acknowledgement

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Table 1. Effect of perampanel for nonepileptic myoclonus in 4 patients with Angelman syndrome

Patient number	Gender	Age at first dosage (years)	Approximate onset of NEM (years)	Other medication	Reduction rate of myoclonus	Side effects	Exposure duration (months)	Latest dose (mg)
1	M	42	26	PIR, VPA	66%	None	19	4
2	F	27	15	PIR, LEV, CZP	99%	Dizziness at 4 mg	19	1
3	F	23	9	VPA, CLB	85%	Possible exacerbation at 4 mg	20	1.2
4	M	31	16	PIR, VPA, CZP	100%	None	16	2

NEM, nonepileptic myoclonus; PIR, piracetam; VPA, sodium valproate; LEV, levetiracetam; CZP, clonazepam; CLB, clobazam.

