리스페리돈 복용 중 발생한 구획증후군을 동반한 횡문근 융해증

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Delayed Onset Rhabdomyolysis and Compartment Syndrome in a Patient on Risperidone

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We report a case of rhabdomyolysis and acute compartment syndrome occurring after an hour of walking in a patient on risperidone for obsessive-compulsive disorder. He was diagnosed with anterior compartment syndrome in the right lower leg and underwent fasciotomies. As sequelae of compartment syndrome, right deep and superficial peroneal neuropathies were identified. In previous cases with risperidone associated rhabdomyolysis, the onset of rhabdomyolysis was mainly related to initiation or dosage increase of risperidone, while the patient of this case had been on a stable dosage of risperidone for more than 6 months. We suspect that genetic variations of 5-HT_{2A} receptor may be related to this difference. Considering rhabdomyolysis and acute compartment syndrome demand earliest interventions to minimize irreversible sequelae, clinicians must have a high index of suspicion without dismissing the possibility of rhabdomyolysis in patients who have been taking risperidone on a stable dosage even for a long time.

Key Words: rhabdomyolysis, risperidone, compartment syndrome

Introduction

Risperidone is an atypical antipsychotic medication for psychiatric disorders. The adverse effects include

extrapyramidal symptoms and increased prolactin levels.¹ Rhabdomyolysis has been rarely reported. Rhabdomyolysis is a condition caused by muscle damage, leading to release of myoglobin and creatine kinase (CK) into the plasma. Although acute kidney injury is a well known severe complication of rhabdomyolysis, compartment syndrome is a severe potential complication.² Compartment syndrome is a disease resulting from myonecrosis within a tight fascial compartment, raising intra-compartmental pressure excessively to compromise local blood flow. The complications in-

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clude loss of limb, deformity, and neural injury.³

Several cases of risperidone associated rhabdomyolysis have been reported.⁴ In most cases, the onset of rhabdomyolysis was mainly related to initiation or dosage increase of risperidone. However, we have recently experienced an unusual case of risperidone associated rhabdomyolysis, occurring without preceding changes of medications or dosages. We report the case presented as an occurrence of rhabdomyolysis and compartment syndrome after an hour of walking in a patient on a stable dosage of risperidone for more than 6 months.

Case Report

A 28-year-old male patient with obsessive-compulsive disorder (OCD) visited the emergency department with right lower leg pain. Besides OCD, he had an unremarkable medical history. His medications included daily dosages of risperidone 3 mg, fluoxetine 80 mg, sertraline 400 mg, clonazepam 0.5 mg, propranolol 20 mg, and clomipramine 25 mg. Risperidone, fluoxetine, clonazepam, and propranolol were initiated 10 months ago. Sertraline was added 6 months ago. Clomipramine was added 2 months prior and the initial dosage had been maintained until recently. All medications except clomipramine had been taken on the same dosages for the past 6 months.

He noticed sudden pain with warmth that started 2 days ago in the right anterior lower leg, but denied any trauma. The pain was developed while he was walking for exercise on level ground at an average speed of 4 km/hour for an hour. He denied any unusual precipitating factors, such as prolonged immobilization, fatigue, or dehydration before the onset. He used to be a social drinker, but he quit it two years ago and had no history of herbal supplements. He used to walk 30 to 60 minutes a day and has not been engaged in any other exercise activities.

On the manual muscle test in his lower extremities, his hip flexors and knee extensors are intact, and his both ankle dorsiflexors, 1st toe extensors and ankle plantar flexors are 1/5 on the right/left side. His CK was 12,012 IU/L (normal range, 20~270 IU/L), AST and ALT were 430 IU/L and 412 IU/L (normal range, 1~40 IU/L), blood urea nitrogen was 12 mg/dL (normal range, 10~26 mg/dL) and creatinine was 1.07 mg/dL (normal range, 0.7~1.4 mg/dL). Under the impression of rhabdomyolysis, magnetic resonance (MR) imaging was done. The MR images of the right lower leg showed marked swelling of the tibialis anterior (TA) and extensor digitorum longus with edematous changes in the perifascial tissues (Fig. 1). He was diagnosed with 'acute compartment syndrome' and underwent fasciotomies (Fig. 2).

Fig. 1. T2-weighted coronal (left) and axial (right) MR images of the right lower leg demonstrate enhancements of the tibialis anterior (arrows) and extensor digitorum longus (arrowheads).

Fig. 2. An urgent fasciotomy with incision of the right lower leg was performed. The anterior compartment muscles were necrotic (arrows).

Table 1. Results of Sensory Nerve Conduction Studies

Nerve	Stimulation site	Recording site	Right				Left			
			Initial (POD 1 mo)		Follow-up (POD 9 mo)		Initial (POD 1 mo)		Follow-up (POD 9 mo)	
			Onset Lat (ms)	Amp (μV)	Onset Lat (ms)	Amp (μV)	Onset Lat (ms)	Amp (μV)	Onset Lat (ms)	Amp (μV)
Superficial peroneal	Below FH	Foot dorsum	NR	NR	2.4	3.7	2.45	12.9	2.45	13.1
Deep peroneal	Ankle	1st web space of foot	NR	NR	NR	NR	2.29	6.0	2.14	12.7
Sural	Calf	Lateral malleolus	2.76	13.2	2.55	11.1	2.50	11.1	2.71	8.3

POD: postoperative day, Lat: latency, Amp: amplitude, NR: no response, FH: fibular head

Table 2. Results of Motor Nerve Conduction Studies

Nerve electrode	Stimulation site	Right						Left					
		Initial (POD 1 mo)			Follow-up (POD 9 mo)			Initial (POD 1 mo)			Follow-up (POD 9 mo)		
		Onset Lat (ms)	Amp (mV)	CV (m/s)	Onset Lat (ms)	Amp (mV)	CV (m/s)	Onset Lat (ms)	Amp (mV)	CV (m/s)	Onset Lat (ms)	Amp (mV)	CV (m/s)
Peroneal-EDB	Ankle	NR	NR	–	NR	NR	–	3.59	4.1	–	3.23	3.8	–
	Below FH	NR	NR	NR	NR	NR	NR	10.83	3.4	47.0	10.57	3.8	47.7
Peroneal-TA	Below FH	2.60	1.7	–	3.13	2.4	–	2.76	7.4	–	2.76	8.0	–
	Above FH	4.27	1.5	54.0	3.96	2.4	48.0	4.38	7.1	55.7	3.96	7.9	50.1
Peroneal-PL	Below FH	3.85	2.6	–	4.11	3.7	–	2.84	5.8	–	3.96	6.1	–
Tibial-AH	Ankle	4.06	17.0	–	3.28	18.0	–	4.27	10.4	–	3.02	13.6	–
	Knee	12.6	12.4	46.8	11.61	15.9	52.8	12.81	7.8	49.2	11.46	11.0	51.0

POD: postoperative day, Lat: latency, Amp: amplitude, CV: conduction velocity, EDB: extensor digitorum brevis, TA: tibialis anterior, PL: peroneus longus, AH: abductor hallucis, FH: fibular head

After the surgery, he began walking on crutches. The CK was gradually decreased. He was referred to a psychiatrist, who recommended to titrate risperidone from 3 to 2 mg/day. After 3 months, the dosage was reduced to 1 mg/day. The sertraline was reduced from 400 to 200 mg/day.

To evaluate nerve injury, an electrodiagnostic study was conducted 4 weeks after surgery. Before the study, we found that the right ankle plantar flexors were recovered to normal, but the ankle dorsiflexors and 1st toe extensors were stationary. Sensory nerve conduction studies (NCS) showed no response in the right superficial and deep peroneal nerves (Table 1). In motor NCS, a compound motor action potential (CMAP) in the right TA was decreased and a CMAP of extensor digitorum brevis (EDB) was not observed. The CMAP of the right peroneus longus (PL) was decreased (Table 2). In electromyography (EMG), the right EDB and extensor hallucis longus showed abnormal spontaneous activities and no activity of motor unit action poten-

Table 3. Needle Electromyographic Examination (POD 1 month)

Muscle	Insertional activity	Fibrillation	Positive sharp wave	Interference pattern
Rt. EDB	Normal	3+	3+	No activity
Rt. EHL	Normal	1+	1+	No activity
Rt. TA	Normal	3+	3+	Reduced
Rt. PL	Normal	0	0	Reduced
Rt. Bic Fem(S)	Normal	0	0	Normal
Rt. Medial GCM	Normal	0	0	Normal

POD: postoperative day, EDB: extensor digitorum brevis, EHL: extensor hallucis longus, TA: tibialis anterior, PL: peroneus longus, Bic Fem(S): Biceps femoris short head, GCM: gastrocnemius

tial. The right TA showed abnormal spontaneous activities and a reduced interference pattern. However, unlike the muscles innervated by the deep peroneal nerve, the right PL showed reduced interference pattern with no abnormal spontaneous activities (Table 3). The patient was diagnosed with right deep peroneal and superficial peroneal neuropathy. After 8 months, the electrodiagnostic study was followed up. Compared previous study, right superficial peroneal neuropathy was well recovered, but right deep peroneal

neuropathy was stationary.

Nine months after the surgery, his right ankle dorsiflexors were still not recovered. However, he could walk alone without assist or aid, although he was uncomfortable.

Discussion

In the present case of spontaneous rhabdomyolysis without any histories of recent trauma or excessive exercise, there was no evidence of any other causes, such as infection, prolonged immobilization, and statin medication. Therefore, it is reasonable to point out risperidone as the most probable cause for rhabdomyolysis. Although some cases have reported that rhabdomyolysis could be developed by SSRI alone,⁵ in that cases, there were preceding factors, such as an excessive exercise, unlike the cases of risperidone associated rhabdomyolysis.

Risperidone is known as a potential risk factor of rhabdomyolysis. One of the known mechanisms of antipsychotics associated rhabdomyolysis is that antipsychotics may increase membrane permeability of skeletal muscle cells, through blockade of 5-HT_{2A} receptors. It can increase the intramuscular calcium level, leading to mitochondrial dysfunction and muscle cell necrosis.⁶

Some cases with SSRI associated rhabdomyolysis have been reported.⁵ Accumulated serotonin by SSRI in skeletal muscle cells may predispose to intramuscular calcium accumulation. Therefore, the combination of risperidone and SSRIs can have synergic effects on the intramuscular calcium accumulation, leading to muscle damage.⁷ Additionally, because risperidone is metabolized by the cytochrome P450 2D6 inhibited by fluoxetine and sertraline, a combination of risperidone, fluoxetine and sertraline can increase blood levels of risperidone,⁸ which could be another synergic mechanism to incur rhabdomyolysis.

From previous cases with risperidone associated rhabdomyolysis retrieved through PubMed search,

certain common characteristics are found as follows. Firstly, the onset of rhabdomyolysis was mainly related to initiation or dosage increase of risperidone. Secondly, there was a co-administration of other medications, such as other antipsychotics and benzodiazepines in most cases. Thirdly, the dosage range of risperidone was between 1 and 8 mg/day, with one over-dose case (96 mg).

Comparing the above characteristics with the present case, the co-administered drugs in our patient, benzodiazepine, SSRI, and tricyclic antidepressant, were relatively common in risperidone-related rhabdomyolysis. His dosage of risperidone, 3 mg/day, was significantly lower than the general dosage of risperidone, 4~16 mg/day and comparably lower than the reported dosages in rhabdomyolysis cases, 1 and 8 mg/day.

The key difference is that the patient in this case had been on a stable regimen in terms of dosage of risperidone and co-administered medications, for more than 6 months. We suspect that this discrepancy of onset is due to the difference in individual responses to risperidone. Lane et al. suggested that polymorphism in the 5-HT_{2A} receptor gene may be associated with risperidone treatment response.⁹ Although it is not certain whether the polymorphism affects cellular responses to the muscle of risperidone, certain genetic variations may be related to the vulnerability to risperidone-associated rhabdomyolysis. If the genetic variations are found, genotyping of 5-HT_{2A} receptor will have predictive values for the development of risperidone-associated rhabdomyolysis. However, it is uncertain whether some genetic factors were associated with risperidone-associated rhabdomyolysis in this case, because the genetic test of 5-HT_{2A} receptor was not performed.

The present case would be informative to clinicians because rhabdomyolysis and compartment syndrome demand earliest interventions to minimize irreversible sequelae. It advises that a clinician must have a high index of suspicion without dismissing the possibility

of rhabdomyolysis in patients who have been taking risperidone on a stable dosage for a long time. In addition, because even low-intensity activity can develop rhabdomyolysis, a clinician must inform the patients of potential risk factors and initial presentations of rhabdomyolysis.

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