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CASE REPORT

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저칼륨혈증성 주기성 마비를 동반한 진행성 근위축증: 증례 보고

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Progressive Muscular Atrophy with Hypokalemic Periodic Paralysis: A Case Report

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Progressive muscular atrophy (PMA) is a rare disease involving lower motor neuron degeneration. Hypokalemic periodic paralysis (HypoPP) is a genetic disorder that causes temporary muscle paralysis due to decreased serum potassium levels. Mutations in the *CACNA1S* gene cause HypoPP. An altered locus closely linked near the *CACNA1S* gene suggests the possibility of motor neuron degeneration. However, PMA with HypoPP is very rare worldwide because HypoPP usually causes progressive muscle weakness involving a form of myopathy without motor neuron disease. In this report, we describe the case of a 64-year-old man who initially complained of weakness in only the left lower extremity, which subsequently progressed bilaterally. Hence, the patient was diagnosed with PMA with HypoPP based on serial electromyography and the presence of a *CACNA1S* mutation. Therefore, serial electromyography is necessary for middle-aged patients with progressive muscle weakness and a history of HypoPP.

Keywords: Muscular atrophy, spinal; Hypokalemic periodic paralysis; Electromyography

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Introduction

Progressive muscular atrophy (PMA) is a rare disease that accounts for approximately 2.5% to 11% of motor neuron disease [1]. In PMA, lower motor neuron (LMN) degeneration occurs which causes isolated LMN symptoms. Patients with PMA have clinical symptoms of progressive weakness, muscle atrophy, fasciculation, and absent or reduced tendon reflexes. PMA is more common in men with a mean age of onset of 63.4 ± 11.7 years [2]. PMA has no biological marker for diagnosis. Therefore, PMA diagnosis is based on clinical symptoms and electrophysiologic features. Electrophysiologic features include LMN dysfunction in 2 or more myotomal distributions and evidence of progressive disease over time [1].

Hypokalemic periodic paralysis (HypoPP), which is an autosomal dominantly inherited channelopathy, represents temporary paralysis with decreased serum potassium level [3]. Symptoms usually begin in puberty and rarely after 25 years of age [3]. A paralytic episode can be precipitated by rest or sleep and the symptoms may be limited to certain muscles or may affect all ex-

tremities. HypoPP diagnosis is based on low serum potassium level during a paralysis event and exclusion of secondary hypokalemia. Frequency of paralytic event is reduced during the third to fifth decades of life; however, some permanent weakness may remain [4]. In a previous study, proximal muscle weakness occurred without paralytic attacks in patients over 50 years old [5]. Similarly, a case of spinal muscular atrophy with HypoPP was shown through clinical and biopsy evidence [6]. However, PMA with HypoPP is not well known, and only few cases had been reported. Here, we report a case which was identified as PMA with HypoPP.

Case Report

A 64-year-old man visited the outpatient clinic due to weakness of the left ankle 3 years ago. The patient had a history of paralysis attacks that improved after potassium injection during puberty. Two of his brothers also had a history of paralytic attacks after sleeping. Manual muscle test (MMT) was performed using a medical research council scale. Motor grade of the left first toe and ankle dorsiflexor muscles were grade 1 with tingling sensation in the entire left lower extremity. Deep tendon reflex (DTR) of the left knee and ankle were considered normal. Upper motor neuron (UMN) signs, including Babinski reflex and ankle clonus, were not observed. Muscle atrophy was observed in the left vastus medialis, tibialis anterior, and extensor digitorum brevis muscles. In a nerve conduction study (NCS), compound muscle action potential (CMAP) amplitudes on tibial and peroneal motor nerves were lower in the left extremity (Table 1). Sensory nerve action potential amplitude and H-reflex on both sides were normal. Upon needle electromyography (EMG), high amplitude and polyphasic motor unit potential with reduced recruitment pattern were observed in the left adductor magnus, vastus medialis, tibialis anterior, and peroneus longus muscles (Table 2). There was no abnormal spontaneous activity in paraspinal muscles. Based on the results, he was diagnosed with left lumbosacral plexopathy. After 2 years, the patient visited the outpatient clinic again due to progressive weakness of both lower extremities. In MMT, motor grade of both ankle and 1st toe dorsiflexor muscles were grade 1. Motor grade of both toe and ankle plantarflexor muscles, and the left knee and hip were grade 2. Other muscles on both lower extremities were grade 3. DTR of both knee and ankle was decreased. In NCS, CMAP amplitudes of both lower extremites were reduced (Table 3). High amplitude and polyphasic motor unit potentials with reduced recruitment pattern were observed in most muscles on both lower extremities and in the right biceps brachii muscle. These suggest dysfunction in cervical distribution as well as lumbosarcral distribution. Abnormal spontaneous activity was observed in some muscles on both lower extremities (Table 4). The patient was admitted with a suspicion of motor neuron disease. Fasciculations over the tongue and both thigh muscles, and hypesthesia on both lower extremities were noted. There were no definite abnormalities causing progressive weakness in the brain or spinal magnetic resonance imaging. There were also no specific findings on abdomen and chest computed tomography. Serum creatinine phosphokinase and thyroid hormone were normal. Antiganglioside antibody and antinuclear antibody were not detected. Pulmonary function was normal, and there was no swallowing difficulty. The patient had no UMN symptoms. Genetic testing identified mutations in the *CACNA1S* gene as the only genetic abnormality. Unlike amyotrophic lateral sclerosis, the patient could be diagnosed with

Table 1. Initial Nerve Conduction Study in both Lower Extremities

Nerve stimulation (record)	Latencies (ms)	Amplitude (μV)	Conduction velocity (ms)
	Distal/proximal	Distal/proximal	
Motor			
Right tibial (AH)	4.3/13.5	7,600/4,100	42
Right peroneal (EDB)	4.7/13.2	1,400/1,200	44
Right peroneal (TA)	4.4/5.7	5,000/3,700	54
Right femoral (VM)	3.6	4,400	-
Left tibial (AH)	4.5/14.1	4,600/3,100	41
Left peroneal (EDB)	-	No response	-
Left peroneal (TA)	3.9/5.5	700/400	50
Left femoral (VM)	3.6	3,200	-
Sensory			
Right sural (ankle)	2.4/3.2	10	47
Left sural (ankle)	2.2/3.0	11	50

AH, abductor hallucis; EDB, extensor digitorum brevis; TA, tibialis anterior; VM, vastus medialis; -, not applicable.

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Table 2. Initial Needle Electromyography in both Lower Extremities

Muscle	Insertion activity	Spontaneous activity			Motor unit potential		
		Fibrillation	PSW	Fasciculation	Duration/amplitude	Phases	Recruitment
Right							
L4/5 paraspinal muscle	Normal	0	0	0	-	-	-
L5/S1 paraspinal muscle	Normal	0	0	0	-	-	-
Left							
Gluteus maximus	Normal	0	0	0	Normal	Normal	Complete
Adductor magnus	Normal	0	0	0	Long/high	Increased	Reduced
Biceps femoris (short head)	Normal	0	0	0	Normal	Normal	Reduced
Tensor fasciae latae	Normal	0	0	0	Normal	Normal	Complete
Iliopsoas	Normal	0	0	0	Normal	Normal	Complete
Vastus medialis	Normal	0	0	0	Long/high	Increased	Reduced
Peroneus longus	Normal	0	0	0	Long/high	Increased	Reduced
Tibialis anterior	Normal	0	0	0	Long/high	Increased	Reduced
Gastrocnemius	Normal	0	0	0	Normal	Normal	Reduced
Extensor digitorum brevis	Normal	0	0	0	-	-	Not detectable
L4/5 paraspinal muscle	Normal	0	0	0	-	-	-
L5/S1 paraspinal muscle	Normal	0	0	0	-	-	-

PSW, positive sharp wave; -, not applicable.

Table 3. Follow-Up Nerve Conduction Study in both Lower Extremities

Nerve stimulation (record)	Latencies (ms)	Amplitude (μV)	Conduction velocity (ms)
	Distal/proximal	Distal/proximal	
Motor			
Right median	3.7/8.2	6,400/5,700	56
Right ulnar	2.67.2	12,000/10,100	59
Left median	4.4/9.4	4,700/4,500	52
Left ulnar	2.6/7.0	8,700/6,100	57
Right tibial (AH)	5.8/17.2	2,000/300	36
Right peroneal (EDB)	9.5/18.3	300/300	40
Right peroneal (TA)	5.9/6.9	600/600	60
Right femoral (VM)	-	No response	-
Left tibial (AH)	5.8/15.3	1,000/900	40
Left peroneal (EDB)	-	No response	-
Left peroneal (TA)	-	No response	-
Left femoral (VM)	-	No response	-
Sensory			
Right median	2.8/4.1	20	51
Right ulnar	2.3/3.1	18	52
Left median	2.8/4.1	31	50
Left ulnar	2.3/2.9	19	52
Right sural (ankle)	2.2/3.1	14	41
Left sural (ankle)	2.2/3.1	11	41

AH, abductor hallucis; EDB, extensor digitorum brevis; TA, tibialis anterior; VM, vastus medialis; -, not applicable.

PMA due to slow-progressing muscle weakness with LMN dysfunction of 2 myotomal distributions (i.e., cervical and lumbosacral) in NCS/needle EMG and tongue fasciculation which is the bulbar symptom (Table 4). Finally, we diagnosed the patient as PMA with HypoPP and treated him with riluzole. The patient was transferred to another hospital after 1 month.

Table 4. Follow-Up Needle Electromyography in both Lower Extremities

Muscle	Insertion activity	Spontaneous activity			Motor unit potential		
		Fibrillation	PSW	Fasciculation	Duration/amplitude	Phases	Recruitment
Right							
Biceps brachii	Normal	0	0	0	Long/high	Increased	Reduced
Flexor carpi radialis	Normal	0	0	0	Normal	Normal	Complete
Abductor pollicis brevis	Normal	0	0	0	Normal	Normal	Complete
1st dorsal interosseous	Normal	0	0	0	Normal	Normal	Complete
Gluteus maximus	Normal	0	0	0	Normal	Normal	Complete
Gluteus medius	Normal	0	0	0	Long/high	Increased	Reduced
Adductor magnus	Increased	0	0	0	Long/high	Increased	Reduced
Iliopsoas	Normal	+	+	+	Normal	Normal	Complete
Tensor fasciae latae	Normal	+	+	+	Long/high	Increased	Reduced
Vastus medialis	Normal	0	0	0	Long/high	Increased	Reduced
Gastrocnemius	Normal	0	0	0	Long/high	Increased	Reduced
Tibialis anterior	Normal	0	0	0	-	-	Poor volition
Biceps femoris (short head)	Normal	0	0	0	Long/high	Increased	Reduced
Semimembranosus	Normal	++	++	++	Long/high	Increased	Reduced
L4/5 paraspinal muscle	Normal	0	0	0	-	-	-
L5/S1 paraspinal muscle	Normal	0	0	0	-	-	-
Left							
Gluteus maximus	Normal	0	0	0	Normal	Normal	Complete
Gluteus medius	Normal	0	0	0	Long/high	Increased	Reduced
Adductor magnus	Normal	+	+	+	Long/high	Increased	Discrete
Iliopsoas	Normal	+	+	+	Normal	Normal	Reduced
Tensor fasciae latae	Normal	0	0	0	-	-	Single MUAP
Vastus medialis	Normal	0	0	0	Normal	Normal	Markedly Reduced
Gastrocnemius	Normal	0	0	0	Long/high	Increased	Reduced
Tibialis anterior	Normal	0	0	0			No volition
Biceps femoris (short head)	Normal	0	0	0	Long/high	Increased	Reduced
Semimembranosus	Normal	++	++	++	Long/high	Increased	Reduced
L4/5 paraspinal muscle	Normal	0	0	0	-	-	-
L5/S1 paraspinal muscle	Normal	0	0	0	-	-	-

PSW, positive sharp wave; MUAP, motor unit action potential; -, not applicable.

Discussion

We report a patient with a history of HypoPP and progressive weakness after middle age. The patient initially complained of weakness on the left ankle. After 2 years, he complained with weakness on both lower extremities. He had characteristic symptoms of isolated LMN lesion and electrophysiologic findings of LMN dysfunction. He also had a characteristic history of paralytic attacks and family history of HypoPP. In genetic testing, *CACNA1S* gene mutation was identified. Finally, we diagnosed the patient as PMA with HypoPP.

When a patient complains of a tongue fasciculation, bulbar symptom and weakness of asymmetrical progressive lower extremity, Kennedy's disease (KD) should be suspected. The disease is a X-linked bulbospinal neuronopathy and characterized by slowly progressive proximal and bulbar weakness, muscular atrophy, muscle pain and gynecomastia [7]. Also the age at onset of KD is in adolescence and ultimately, the diagnosis is confirmed through genetic testing that shows an expansion of polymorphic tandem CAG repeat in the first exon of the androgen receptor gene [7]. The middle-aged patient in our case showed no gynecomastia and the only *CACNA1S* gene mutation was identified in genetic testing. Therefore, we could rule out the KD.

HypoPP is mostly caused by gene mutation of the calcium channel *CACNA1S*, R528H, and R1239H. Approximately 80% of these gene mutations result in late onset myopathy [8]. In this case, the patient had the *CACNA1S* mutation leading to a diag-

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nosis of HypoPP. The *CACNA1S* mutation involves the membrane of the transverse tubular system and causes abnormalities in muscle contraction and relaxation [8]. According to a previous molecular research on PMA, TAR DNA-binding protein 43 (TDP-43)-positive inclusions were associated with isolated LMN degeneration without UMN symptoms [9]. However, only few PMA cases had TDP-43 mutations. The pathogenesis of PMA is not well known which makes diagnosis more difficult. Therefore, other LMN syndromes should be excluded for PMA diagnosis, which is delayed for an average of 23 months after symptom onset.

A previous case report described PMA with HypoPP caused by *CACNA1S* gene mutation [8]. They suggested that an altered locus, which is closely linked near CACNA1S, has the capability to produce motor neuron degeneration. No further cases on PMA with HypoPP have been reported worldwide. Our study supports the possibility that the *CACNA1S* gene may be involved in development of PMA. Hence, further molecular research is needed on how this gene is involved in development of PMA.

The relationship between PMA and HypoPP is not well known. When a patient with a past history of HypoPP complains of muscle weakness, myopathy is suspected. Myopathy after HypoPP is relatively well known, and diagnosis is based on characteristic findings of myopathy in EMG [10]. Myopathy in HypoPP can occur independent of paralytic attacks, and progressive weakness may occur, especially in proximal muscles of the lower extremities. However, the patient initially complained of distal weakness without characteristic findings of myopathy on EMG. During initial EMG, he was misdiagnosed with a left lumbosacral plexopathy. It was difficult to diagnose PMA because the patient's initial symptom was weakness on unilateral lower extremity, and there was no abnormal spontaneous activity on paraspinal muscles. After 2 years, the weakness progressed to both lower extremities, and we diagnosed him with PMA and characteristic findings of LMN degeneration based on EMG. Therefore, if a patient with history of HypoPP develops progressive muscle weakness after middle age, serial EMG should be performed. Follow-up of the weakness symptoms should be performed to determine if a new abnormality occurred.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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