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A CASE OF LOW PHOSPHORYLASE B KINASE ACTIVITY WITH BIPHASIC PERIODIC PARALYSIS: PHOSPHORYLASE B KINASE CONVERSION ABNORMALITY

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We evaluated a 12-year-old boy with repeated transient episodes of flaccid skeletal muscle paralysis, affecting mainly the trunk and proximal limbs, and eyelid myotonia. These symptoms had manifested in infancy and followed a course of slowly progressive muscle weakness. Serum CK was elevated to more than twice the upper limit of normal. His muscle weakness was induced by a short rest after exercise, and the eyelid myotonia by exposure to cold. Both hypokalemic and hyperkalemic periodic paralysis attacks could be induced by loading tests. Phosphorylase (−AMP) activity in biopsied quadriceps femoris muscle was 1.0 nmol/min/mg protein (control 3.10 ± 1.6), and two separate measurements of the active form of muscle phosphorylase b kinase activity yielded values of 19.2 and 22.5 unit/min/g protein (control 59.5 ± 15.8). Total muscle phosphorylase b kinase measured in the presence of Ca^{2+} and cAMP was normal. Erythrocyte and leukocyte phosphorylase b kinase activities were normal. The co-existence of low phosphorylase b kinase activity and clinical manifestations, including Ca^{2+} responsiveness, suggested a cAMP or Ca^{2+} dysfunction in this patient.

Introduction

Phosphorylase b kinase catalyzes the conversion of phosphorylase b to phosphorylase a. Human phosphorylase b kinase deficiency has been documented in muscle, liver, and red blood cells. However, a reliable classification of phosphorylase b kinase deficiency has not yet been established. We report the first case of low phosphorylase b kinase activity with biphasic periodic paralysis.

Case

A 12-year-old boy was referred to the Department of Pediatrics, Tokyo Women's Medical College Hospital, with a chief complaint of difficulty in walking. The patient was born after a full-term pregnancy and vacuum extraction delivery, and his perinatal development was uneventful. There was no consanguinity in his family and he had a healthy elder sister. Birth weight was 3,400 g and neonatal course was uneventful. Motor development was essentially normal; head control at 3 months, maintenance of sitting posture at 6 months, initial walking at 1 year and 3 months.

However, his parents were aware that he experienced episodes of flaccid paralysis of sudden onset rendering him unable to crawl on his hands and knees or raise his head. He completely recovered from these episodes within several hours to a few days, and none were associated with sensory disturbance. Mental development was

normal.

There was no past history of trauma or central nervous system infection preceeding these episodes. In early childhood, he was seen at another hospital because of an episode of inability to walk. Mild elevation of serum muscle enzymes, calf muscle hypertrophy and ankle joint contracture of unknown origin were noted by the examining physician. The patient experienced repeated episodes of limb weakness after short periods of rest, following walking or running. He could not, for example, stand up from the sitting position after riding in a train or sitting on a chair. A brief rest after strenuous exercise rendered him unable to stand unaided. The attacks lasted several hours to a few days during the early years of his clinical course. The muscle weakness appeared to abate, with the patient recovering to his previous condition, after each episode.

On other occasions, he noted bilateral myotonia of the eyelids for a few seconds which seemed to be induced by cold and was unrelated to his limb weakness. These episodes usually occurred after he had washed his face with cold water, or been swimming or riding a bicycle in cool weather.

He experienced episodes of generalized weakness and respiratory distress with diaphoresis: he awoke from sleep because of a feeling of discomfort and inability to perform the chest wall movement necessary for respiration. He was unable to cough or move, and had neck, chest and extremity stiffness. The stiffness disappeared with passive movement initiated by his mother who came to his room within a few minutes in response to his shouting. These episodes resolved spontaneously and occurred approximately once a month.

On the day after coming back from a school trip of a few days duration, he was able to play soccer
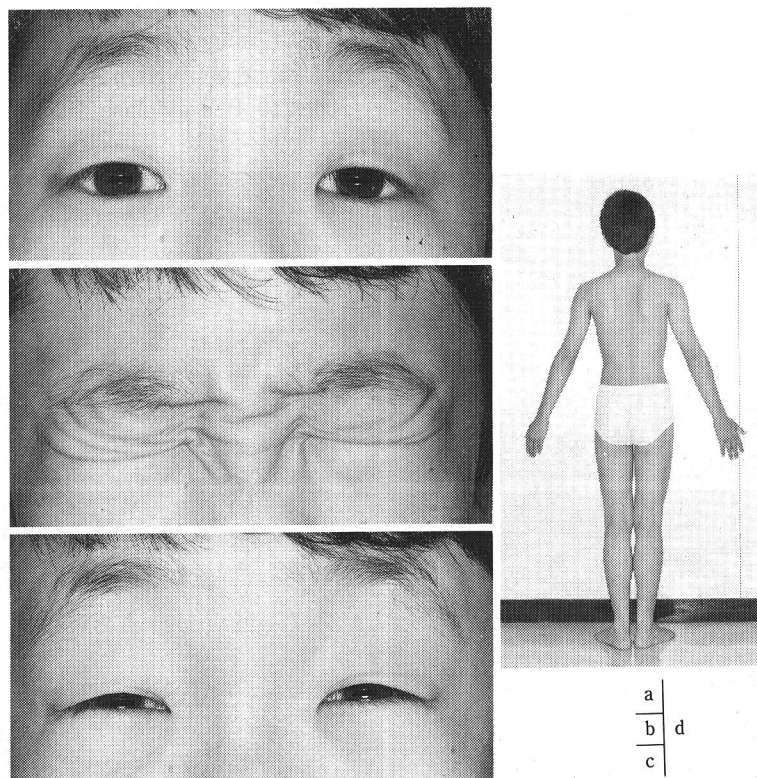

Fig. 1 Patient at age 12
a: eyes open, b: closing the eyes firmly, c: followed by difficulty reopening the eyes, d: moderately well developed 12 year old boy, without anomalies, muscle atrophy or pseudohypertrophy.

but complained of proximal leg pain the next morning and needed support to stand up. He was completely unable to run. His parents, therefore, brought him to our hospital and he was admitted for detailed evaluation. He had never noticed discolored urine or experienced macrohematuria.

Physical examination on admission (Fig. 1) revealed a moderately well proportioned boy with a long face but no apparent anomalies. Neither cardiomegaly nor hepatomegaly was present. He

had a waddling gate and could not walk on his heels. Neurological examination revealed a mildly lax shoulder girdle, and muscle weakness of the proximal extremities and neck. Manual muscle testing results are shown in Table 1. Mild joint contracture was apparent with dorsiflexion of the ankle and hip extension, and decreased or diminished deep tendon reflexes were also noted. To stand up from the supine position, he rolled over to a prone position and raised his body using his arms, then stood up as if to climb up by himself putting his hands on his knees (Gowers' sign). Neither percussion myotonia nor grip myotonia was elicited. It was difficult for him to reopen his eyes fully after he had closed them firmly, because of the myotonia. Cranial nerve functions were normal. Neither sensory disturbance nor cerebellar signs were noted. His IQ was 117 by TK Binet.

Laboratory Findings

Serum CK was between 623 and 259 mU/ml (normal range 28~124 mU/ml). GPT 26 KU (normal range 0~19 KU), ALP 955 IU (normal range 200~710 IU), aldolase 10.6 IU/l (normal range
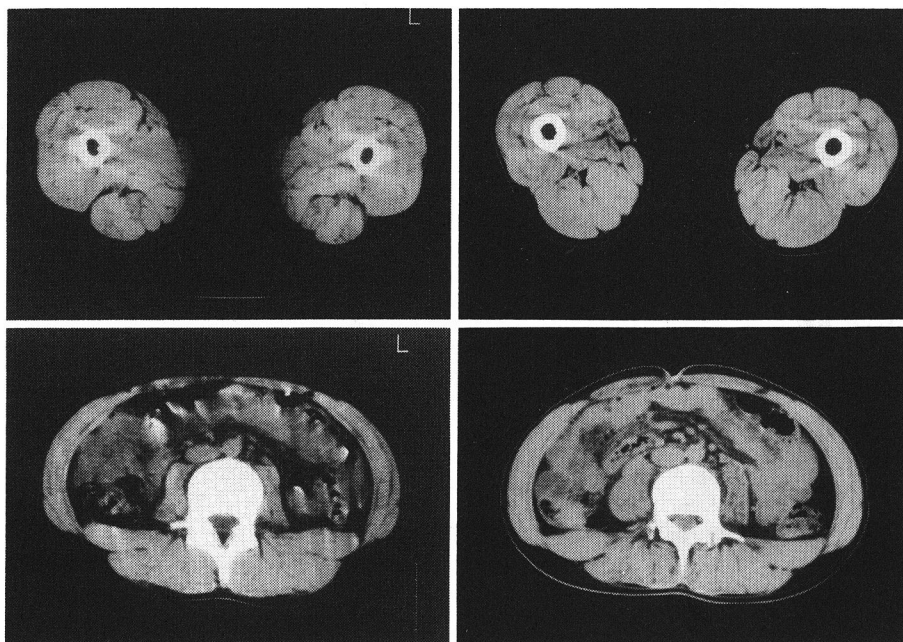
Table 1 Manual muscle testing results expressed using the scale of the Medical Research Council (1976) Aids to the Examination of the Peripheral Nervous System Memorandum No 45 (H.M.S.O.: London)

Muscle	Grade	Muscle	Grade
Neck anteflexion	2	Palmar flexion	4
retroflexion	4	Dorsiflexion	4
Deltoideus	3	Psoas	3
Pectoralis major	5	Quadriceps femoris	4
Biceps	4	Gluteal	4
Triceps	4	Gastrocnemius	5
Pronator	4	Tibialis anterior	3⁻
Supinator	4		

Fig. 2 Muscle CT of this case
left: 12Y, right: 16Y.

2.2~7.3 IU/l), reticulocyte 16% (normal range 3~11%) and urine creatinine 1.41 mg/dl (normal range 0.31~1.10 mg/dl).

There was no evidence of hemolysis.

The following laboratory parameters were within normal range; total serum protein, serum electrolytes (including potassium 4.3 mEq/l), GOT, γ-GTP, LDH, hemogram, T3, T4, TSH, aldosterone, complements, immunoglobulins, cellular immunity, blood gas analysis, lactate, pyruvate, urinalysis and urine organic acid analysis.

EMG: A dive bomb sound was found in the opponens pollicis muscle at the insertion but no fibrillation activity was noticed. Interference was normal. EMG of other muscles of the upper and lower limbs were normal.

Muscle CT (Fig. 2): Muscle CT at age 12 revealed normal density and mass volume of muscles of the trunk, limbs and face. Another scan, obtained four years later at age 16, revealed mildly atrophic muscles and patchy low density areas in the psoas, rectus femoris and sartorius muscles.

Histology (Fig. 3): Many muscle fibers revealed round areas of decreased activity with NADH-TR in the central portion of each muscle fiber (core). These cores showed basophilic staining with H&E and Gomori-trichrome stains, and were often posi-
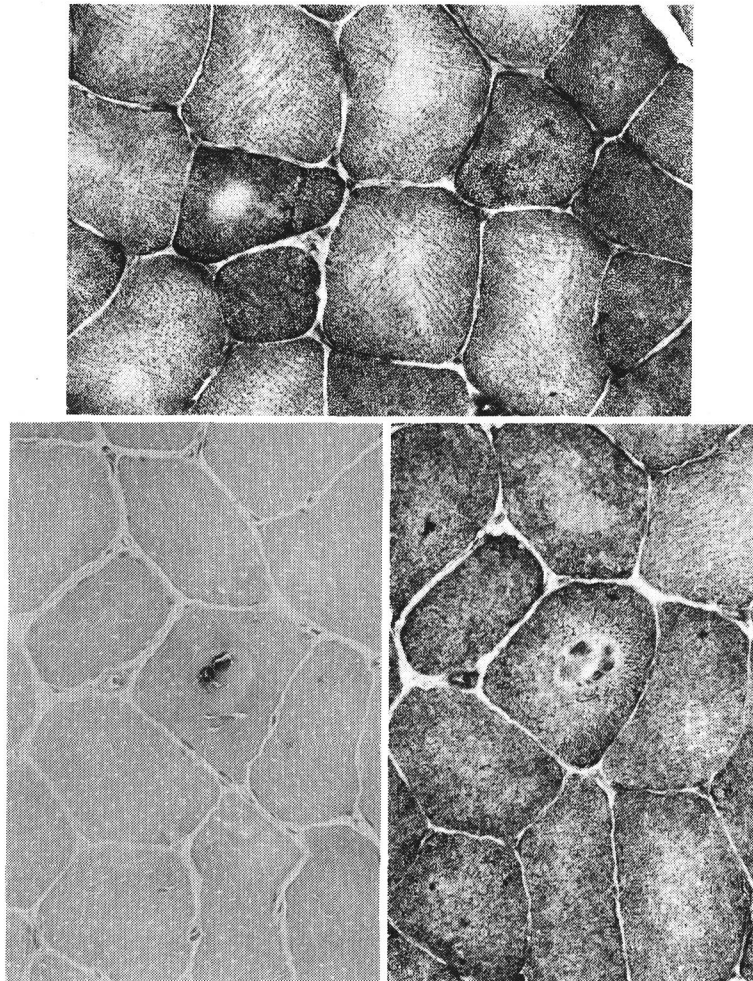

Fig. 3 Muscle biopsy
a: cores with NADH-TR ×100, b: core was positive for acid phosphatase ×100, c: NADH ×100.

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tive for acid phosphatase activity. Occasionally there were small vacuoles, some of which were positive for acid phosphatase activity. Most muscle fibers also showed irregular staining with NADH-TR and PAS. Modified ATPase revealed a type 2b fiber deficiency.

Electron microscopic study (Fig. 4) showed patchy myofibrillar degeneration (mini-cores).

Sarcoplasmic reticulum was often dilated in and around these lesions and glycogen granules were abundant. There were also irregular, membrane-bound vacuoles, occasionally accompanied by lysosomes. These vacuoles seemed to be related to the sarcoplasmic reticulum (arrows).

Electrophysiological study (Fig. 5): With repetitive supramaximal stimulation of the digitales
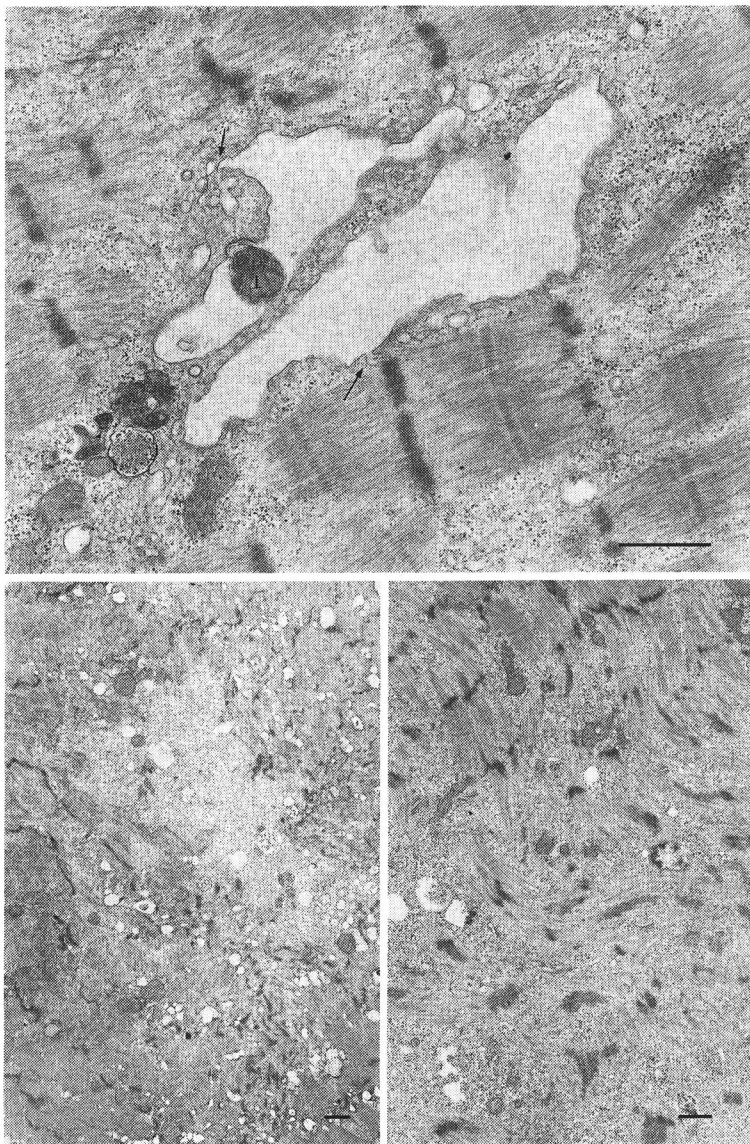
a

b | c

Fig. 4 Electron micrograph
a: irregular dendritic shaped vacuoloes related to sarcoplasmic reticulum L; lysozome, b: milder change than in (a), c: core formation.
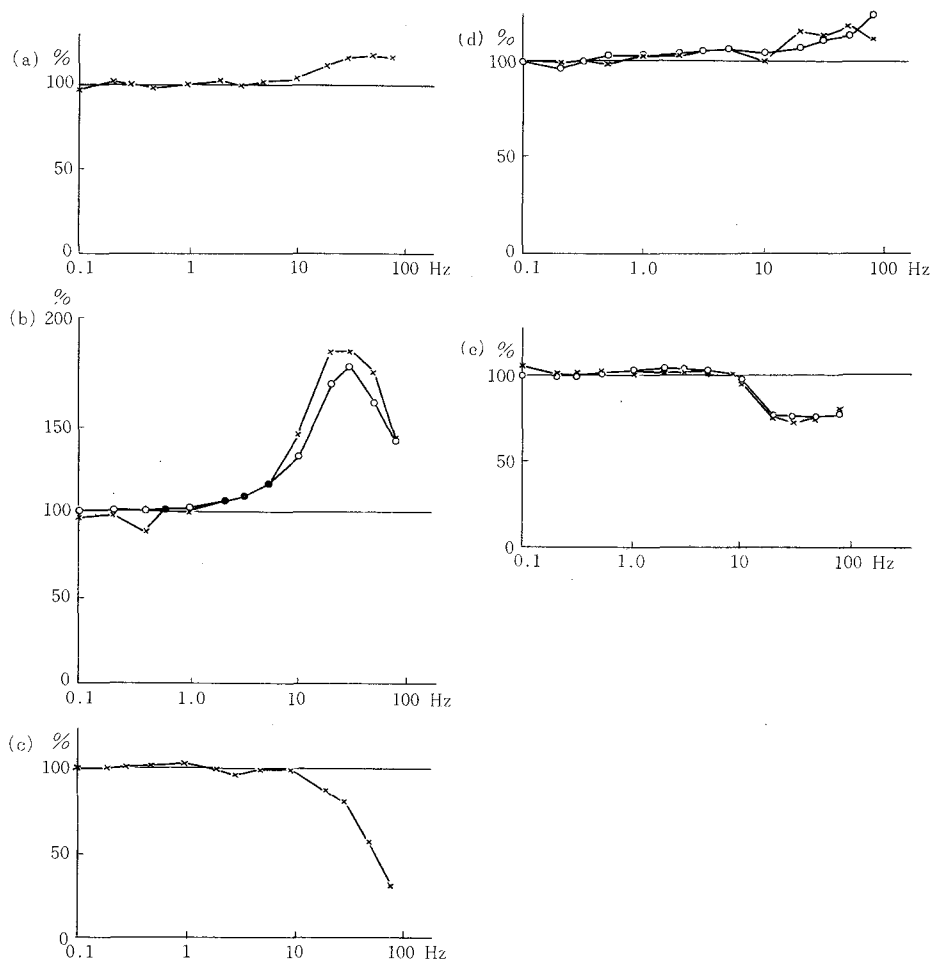
Fig. 5 Repetitive supramaximal stimulation study

abscissa: stimulation frequency, ordinate: amplitude of first M wave response as a percentage of the fifth M wave response.

Condition: (a) warming, (b) normal room temperature, (c) cooling, (d) calcium gluconate administered intravenously and (e) sodium chloride solution administered intravenously.

palmares communes nerve at a frequency of 0.1~80 Hz, an M wave was recorded from the right abductor pollicis brevis muscle. At each frequency tested, the ratio of the amplitude of the fifth to first M wave response, from five consecutive stimulations, was plotted (Fig. 5).

A decremental response was observed with 30~80 Hz stimulation while the patient's right hand was cooled to about 32.5~28.3°C (Fig. 5c). An incremental response, which was maximal at 20~30 Hz stimulation, was seen without cooling (Fig. 5a, b). Testing conducted under conditions of continuous intravenous calcium gluconate or warming of the right hand produced a mildly incremental response with frequent stimulation (Fig. 5d). Testing with continuous intravenous sodium chloride solution infusion (Fig. 5e) decreased the M wave response to 30~60 Hz stimulation. Muscle power was examined on each occasion, and power was found to be maximal immediately after intravenous administration of calcium gluconate. Cooling had the most detrimental effect on muscle power.

Loading test: During glucose testing, the lactate

concentration increased from a fasting value of 10.7 mg/dl to 20.9 mg/dl.

Glucagon given intramuscularly raised the serum glucose level from 83 mg/dl to 168 mg/dl, simultaneously with an increase in blood lactate level from 9.7 mg/dl to 11.8 mg/dl.

Forearm ischemic exercise testing (Fig. 6) resulted in a slight elevation of blood lactate, from 11.9 mg/dl to 19.0 mg/dl, and a normal increase in the NH₃. KCL loading test result is shown in Fig. 7. Repetitive, transient lid lag of 10 sec to 10 min duration was observed during the first hour following KCl administration. One hour after KCl administration, he complained of difficulty coughing, was unable to breathe deeply and had marked limb muscle weakness, at which time the serum potassium level was 5.0 mEq/l.

Muscle weakness was induced by a challenge test, consisting of prolonged glucose administra-

tion (Fig. 8) (50 g every hour for 15 hours)[1], and reduction of the serum potassium level to 2.9 mEq/l. Four hours after beginning the oral glucose administration, he complained of generalized
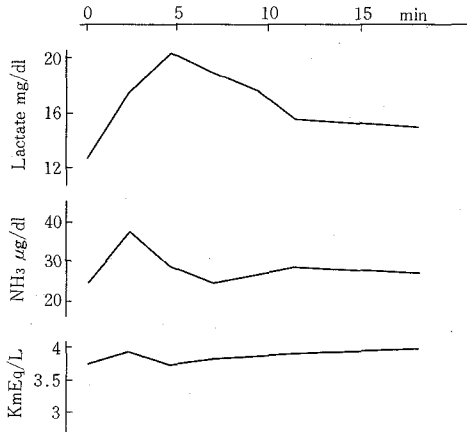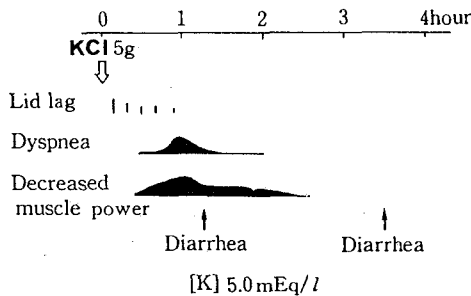
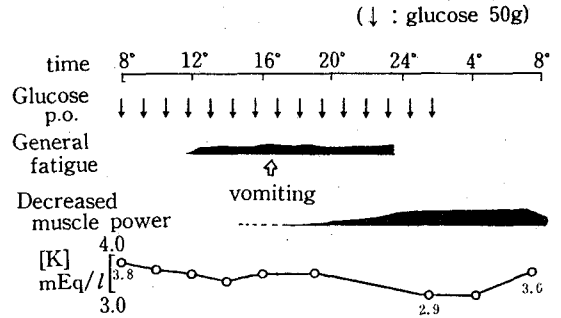Fig. 6 Ischemic exercise test

Fig. 7 KCl loading test

Fig. 8 Prolonged glucose loading test

Table 2 Glycolytic muscle study

a : glycolytic muscle enzymes : activities are expressed as nmoles of substrate utilized/min/mg protein : mean±SD

	patient	control
phosphorylase(−AMP)	1.0 : 0.9	3.10±1.6
phosphorylase(+AMP)	58.0 : 67.7	44.7±19.6
phosphoglucomutase	296.5	261.1±70.1
phosphohexoisomerase	770.8	838.9±221.1
phosphofructokinase	15.8	19.9±11.1
aldolase	415.1	380.6±112.0
glyceraldehyde-3p-dehydrogenase	924.9	1,708.1±536.6
phosphoglycerate kinase	830.1	770.6±172.8
phosphoglycerate mutase	1,138.4	820.4±191.3
enolase	296.5	331.3±64.3
pyruvate kinase	1,067.3	991.2±292.2
LDH	1,423.1	1,302.4±517.5
debranching enzyme	14.1	21.7±7.7

Activities are expressed as nmoles of substrate utilized/min/mg protein : mean±SD

b : Phosphorylase b kinase activities in muscle. leucocytes and erythrocytes.

		patient	control
muscle (unit/min/g protein)	total[1]	82.1	70.1±16.6
	active[2]	19.2 : 22.5	59.5±15.8
leucocyte (unit/min/g protein)	total[1]	48.1	52.1±7.9
	active[2]	39.1	47.2±4.1
erythrocyte (unit/min/g Hb)	active[2]	1.9	1.8±0.3

[1] ; measured in the presence of 10 μmol CaCl₂ and 1 μmol cAMP, [2] ; measured in the absence of CaCl₂ and cAMP.

fatigue. Muscle weakness manifested 10 hours after beginning this test, and lasted for 14 hours. He could move neither his limbs nor his trunk against gravity.

His eyelid lag could also be induced by putting his feet in 4°C water or having him hold an ice bag in his hands.

Biochemical analysis of glycolytic enzymes in biopsied muscle and blood cells (Table 2): An in vitro anaerobic glycolysis study showed a block after glycogen and before glucose-6-phosphate.

Direct measurement of individual glycolytic enzymes in the patient's muscles demonstrated a partial deficiency, at 30% of the control phosphorylase activity value (in the absence of AMP). The active form of phosphorylase b kinase (Pbk) (in the absence of cAMP and $CaCl_2$) was also decreased.

Discussion

This patient suffered from episodes of both hypokalemic and hyperkalemic periodic paralysis,

Table 3 Reported cases of muscle phosphorylase b kinase deficiency

Age	Sex	Onset	Limb weakness hypotonia	Cramp Stiffness (onset age)	Hepato-megaly	Short stature	Others	Combined enzyme deficiencies	Mode of inheritance	Author
					Muscle					
1Y	F	0Y	+						Unknown	Ohtani et al[13] (1982)
1Y	F	0Y	+h		.			debranching enzyme	Unknown	Iwamasa et al[14] (1983)
4Y	F	2Y	+				MR, Growth retardation	phosphofructokinase	Unknown	Danon et al[15] (1981)
17Y	F	5Y	+w						Unknown	Iwamasa et al[14] (1983)
17Y	F	2Y	+w	+c(2Y)					Unknown	Marume et al[16] (1983)
26Y	M	6Y		+(6Y)					Unknown	Clemens et al[17] (1990)
31Y	F	Childhood	+w	+(Childhood)					Unknown	Carrier et al[18] (1990)
35Y	M	35Y		+(35Y)					Unknown	Abarbanel et al[19] (1986)
58Y	M	46Y	+w						Unknown	Clemens et al[17] (1990)
12Y	M	0Y	+	+(10Y)					Unknown	our case
					Muscle and Liver					
4Y	M	1Y	+h		+	+	Doll face		AR	Lerner et al[7] (1982)
5Y	F	0Y			+		Round face		AR	Lerner et al[7] (1982)
10Y	F	0Y			+		Round face		AR	Lerner et al[7] (1982)
7Y	M	0Y	+w		+	+	Doll face		AR	Madlom et al[8] (1989)
4Y	M	?Y	+		+	+	Doll face 6 and 11y.o. sisters		AR	Bashan et al[9] (1981)
5Y	M	?Y			+				AR	Lederer et al[10] (1980)
?Y	M	?Y	+h		+		Developmental delay		Unknown	Kikuchi et al[11] (1988)
?Y	M	?Y	+w		+		Growth retardation		Unknown	Besley et al[12] (1987)
					Heart					
4M	F								Unknown	Servidi et al[20] (1988)
5M	M								Unknown	Mizuta et al[21] (1984)

+ ; hypotonia+weakness, +h ; hypotonia only, +w ; weakness only.

known as biphasic periodic periodic paralysis[2]. The results of biochemical tests indicated a low muscle Pbk (active form) activity, although total Pbk was within normal range. In most previously reported cases of Pbk deficiency, the liver was affected[3]~[6]. A few cases in which both liver and muscle[7]~[12], or only muscle[13]~[19], were affected have also been reported. Liver biopsy was not performed in our patient as there was no hepatosplenomegaly and liver functions were normal except for mild elevation of GPT without elevation of GOT. In addition, erythrocyte and leukocyte Pbk activities were normal. Nine myopathy cases with Pbk deficiency and other enzyme deficiencies, such as glycogen storage diseases, have been reported[13]~[19]. Neither debranching enzymes nor myophosphorylase activity were affected in our patient, suggesting that this case had an isolated low muscle Pbk activity. In previous reports, clinical symptoms of Pbk deficiency included muscle weakness and hypotonia, as in our patient. Weakness was the main symptom in infancy and early childhood. Painful muscle cramps[16] and an autosomal recessive inheritance[7]~[9] pattern have also been reported. After adolescence, cramps and exercise intolerance appeared. Unlike most previously reported cases, in which muscle weakness appeared simultaneously with cramps and stiffness, our patient showed intermittent muscle weakness before one year of age but did not develop cramps and stiffness until age 10.

Periodic paralysis is generally classified as hypokalemic, hyperkalemic or normokalemic type, and is characterized by transient attacks of muscle weakness[22]. A common underlying pathophysiologic mechanism affecting the muscle membrane has been sought in all three types. In familial hyperkalemic periodic paralysis, particularly, a human skeletal muscle sodium gene located on 17q23.1-25.3 has been reported[23]. In other types of periodic paralysis, including that of our case, an ion channel mechanism is currently under discussion.

Our review of the literature on diseases underlying periodic paralysis yielded one report of a generalized metabolic disorder with periodic paralysis due to AMP-deaminase deficiency[24]. To our knowledge, however, low Pbk activity with periodic paralysis has not previously been reported.

The reaction sequence for the activation of phosphorylase in skeletal muscle is: 1. epinephrine triggers the activation of adenylate cyclase, 2. adenylate cyclase catalyzes the formation of cAMP from ATP, 3. cAMP activates a cAMP-dependent protein kinase, and 4. this protein kinase phosphorylates Pbk, resulting in the activation of phosphorylase. Furthermore, it should be noted that Ca^{2+} and cAMP is necessary for the activation of Pbk.

In the present case, although Pbk activity measured in the absence of Ca^{2+} and cAMP was low, the reaction sequence described above seemed to be normal, since the total Pbk value measured in the presence of Ca^{2+} and cAMP was normal. These data indicate that conversion from the inactive to active form of Pbk was disturbed in this case, due to either decreased Ca^{2+} concentration or decreased cAMP concentration or both in the cytoplasm.

In the present study neither Ca^{2+} concentration nor cAMP concentration was measured. However, improvement in muscle power and electrophysiological responses after Ca^{2+} administration, and dilated sarcoplasmic reticulum suggest that Ca^{2+} regulation might be involved.

The other possible mechanism is decreased cAMP concentration. Since activation of cAMP-dependent kinase is related to activation of adenylate cyclase and ATP, a defect in this pathway, for example, in the adrenaline receptor, stimulatory G protein (Gs) or GTP, is possible in this case.

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低カリウム性および高カリウム性周期性四肢麻痺を伴った

ホスホリラーゼ b キナーゼ活性低下例

―ホスホリラーゼ b キナーゼ変換異常―

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鈴木　典子・大澤真木子・宍倉　啓子　・鈴木　暘子

新井　ゆみ・福山　幸夫・杉江　秀夫＊・鶴井　聡＊

一過性に，主に体幹と近位筋の麻痺と，眼瞼ミオトニアを反復する12歳の男児について報告する．

乳児期に発症し，徐々に筋力低下が進行してきた．血清 CK は，正常の倍以上に上昇していた．運動後の休息の後で筋力低下をみたり，寒冷下で眼瞼ミオトニアが起こった．各種の負荷試験により，低カリウム・高カリウム両者の周期性四肢麻痺の発作が誘発された．

大腿四頭筋でのホスホリラーゼ（−AMP）活性は，1.0nmol/min/mg 蛋白（正常3.10±1.6），活性型筋ホスホリラーゼ b キナーゼは，19.2と22.5units/min/g 蛋白（正常59.5±15.8）であった．赤血球と白血球のホスホリラーゼ b キナーゼ活性は各々正常であった．

本例におけるホスホリラーゼ b キナーゼの活性の低下と周期性四肢麻痺症状との共存は，細胞内の Ca^{2+} あるいは cAMP の調節異常によると考えられた．