expansive intraperitoneal bleeding caused by rupture of the right hepatic capsule (Fig. 2c). Multiple variable-sized cystic blood-filled spaces and hemorrhagic necrosis were found in the liver (Fig. 2d). Histopathologically, the liver contained multiple blood-filled spaces (Fig. 2e) that were devoid of CD31-positive endothelial lining (Fig. 2f), which was compatible with peliosis hepatis.

3. Discussion

Peliosis hepatis is a rare fatal disorder with a number of causes, and is defined as multiple, variable-sized, cystic, blood-filled spaces through the liver parenchyma, in which spaces are not covered by endothelium of blood vessels histopathologically [9]. Peliosis hepatis has mostly been reported in adult patients associated with chronic wasting disorder [10], human immunodeficiency virus infection [11–12], oral contraceptives [13], androgenic steroids [14], and *Bartonella henselae* infection [15], and is idiopathic [16]. In children, peliosis hepatis is rare and has only been reported with androgenic steroids [17–18], *Escherichia coli* pyelonephritis [19], and XLMTM [4–7].

In XLMTM, only six children with peliosis hepatis, including our case, have been reported (Table 1) [4–7], and five of them developed acute onset multiple organ failure. The remaining child was detected by chance at the time of the autopsy, and this child had a central nervous system malformation and hydrocephalus with ventriculo-peritoneal shunting, and died of a hypoxic episode at 4 years old. The mean age at onset of peliosis hepatis was 4 years. Antecedent infection before hepatic hemorrhage was observed in three patients, including our patient. An elevated liver function test was observed in three patients, including our patient, but was normal in two. Five of six patients died of acute fatal hepatic hemorrhage. One patient survived after laparotomy and transarterial embolization [5]. Therefore, peliosis hepatis with XLMTM is characterized by difficult-to-treat acute onset. Some adult patients with idiopathic peliosis hepatis have received successful emergent hepatectomy, liver transplantation, and arterial embolization [16,20]. However, once hepatic hemorrhage from peliosis hepatis occurs, it is usually difficult to control bleeding, as observed in our patient. Therefore, reducing the incidence and prompt recognition of hepatic hemorrhage are mandatory for XLMTM patients.

The diagnosis of peliosis hepatis is difficult and often missed or delayed because of the atypical findings on standard radiological tests. A previous report indicated that ultrasonic examination is useful to detect abnormal findings according to various liver conditions, and can show perinodular and intranodular vascularity in patients with peliosis hepatis [21]. Other imaging systems, including CT, magnetic resonance imaging, and angiography can also be helpful for diagnosis of peliosis hepatis [18,21]. Our patient showed persistent mild elevations in a serum liver function test before the episode of acute hemorrhage. He had not received a routine ultrasonic examination, and CT findings on admission indicated no hepatic lesion, suggesting hemorrhage or peliosis hepatis. Therefore, fatal hepatic hemorrhage from peliosis hepatis was induced by an unknown cause after admission.

The mechanism of peliosis hepatis remains to be fully elucidated. And the causal relationship between peliosis hepatis and XLMTM is poorly understood, although MTM1 protein expression in liver are reported in GeneCards®. It has been reported that a mechanical in-exsufflator (MI-E) is safe and effective for respiratory infections of pediatric patients with neuromuscular disorders [22]. MI-E was initially used for removing secretions in our case, and fatal hepatic hemorrhage occurred on the next day of MI-E adoption. In some reports describing the mechanism of peliosis hepatis, blockade of liver blood outflow and increased sinusoidal pressure in patients with abnormality of the sinusoidal barrier were important factors contributing to the pathogenesis [23,24]. In our case, there were no

Table 1
Summary of peliosis hepatis in XLMTM patients.

No.	Age	Severity of XLMTM	Cognitive development	Detection of PH	Known liver dysfunction	Infection at the onset of PH	Diagnosis	Status
1[4]	5 y	Severe	Normal	Hepatic hemorrhage	Yes	Un-documented	Autospy	Deceased
2[4]	4 y	Severe	Normal	By chance (autospy)	No	Un-documented	Autospy	Deceased
3[5]	3 y	Severe/ moderate	Normal	Hepatic hemorrhage	No	URI otitis media	CT	Improved
4[6]	2 y 6 m	Severe	Un-documented	Hepatic hemorrhage	(Un-documented)	Un-documented	Autospy	Deceased
5[7]	5 y	Severe	Un-documented	Hepatic hemorrhage	Yes	Fever	Autospy	Deceased
6 (present patient)	5 y	Severe	Slightly retarded	Hepatic hemorrhage	Yes	Pneumonia	Autospy	Deceased

PH: peliosis hepatis, URI: upper respiratory infection, CT: computed tomography.

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manifestations of a blockade of liver blood outflow, but the elevation in inferior vena cava pressure caused by a sharp rise in intrapleural pressure using MI-E might have been a potential cause of peliosis hepatis.

In conclusion, peliosis hepatis is a rare but important fatal complication that may occur more often once genetic or other therapies for XLMTM become available with a resulting increase in life expectancy. To avoid fatal hepatic hemorrhage from peliosis hepatis, routine liver function tests and abdominal imaging studies are recommended for all XLMTM patients. In addition, it might be necessary to carefully check liver imaging tests, especially at the time of using mechanical ventilation.

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Case report

Muscle glycogen storage disease 0 presenting recurrent syncope with weakness and myalgia

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Abstract

Muscle glycogen storage disease 0 (GSD0) is caused by glycogen depletion in skeletal and cardiac muscles due to deficiency of glycogen synthase 1 (GYS1), which is encoded by the *GYS1* gene. Only two families with this disease have been identified. We report a new muscle GSD0 patient, a Japanese girl, who had been suffering from recurrent attacks of exertional syncope accompanied by muscle weakness and pain since age 5 years until she died of cardiac arrest at age 12. Muscle biopsy at age 11 years showed glycogen depletion in all muscle fibers. Her loss of consciousness was gradual and lasted for hours, suggesting that the syncope may not be simply caused by cardiac event but probably also contributed by metabolic distress.

Keywords: Glycogen storage disease; Glycogen synthase; Glycogen; Syncope; Sudden death

1. Introduction

Glycogen is a high molecular mass polysaccharide that serves as a repository of glucose for use in times of metabolic need. It is stored in liver, cardiac and skeletal muscles, and broken down to glucose to produce ATP as energy as needed. For the synthesis of glycogen, at least two proteins, glycogenin (GYG) and glycogen synthase (GYS), are known to be essential. GYG is involved in the initiation reactions of glycogen synthesis: the covalent attachment of a glucose residue to GYG is followed by elongation to form an oligosaccharide chain [1]. GYS catalyzes the addition of glucose monomers to the growing glycogen molecule through the formation of alpha-1,4-glycoside linkages [2].

Defect in either GYG or GYS can cause glycogen depletion. Recently, muscle glycogen deficiency due to a mutation in a gene encoding muscle GYG, *GYG1*, was reported [3] and named as glycogen storage disease type XV. In contrast, glycogen depletion caused by the *GYS* gene mutation is called glycogen storage disease type 0 (GSD0). GSD0 was first reported in 1990 in patients with type 2 diabetes who had a defect in glycogen synthesis in liver, which was caused by a defect in liver GYS, GYS2, and the disease was named as liver GSD0 (or also called GSD0a) [4,5].

The disease of muscle GYS, GYS1, was first described in 2007 in three siblings and named muscle GSD0, which is

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also called GSD0b [6]. One of the patients initially manifested exercise intolerance, epilepsy and long QT syndrome since the age of 4 years, then died of sudden cardiac arrest after exertion when he was 10.5-year-old. The other two siblings were then genetically confirmed as muscle GSD0 with mutations in *GYS1* and cardiac involvement was also found in both. The second muscle GSD0 family was reported in 2009 [7]. The 8-year-old boy had been healthy before collapsing during a bout of exercise, resulting in death. Post-mortem examinations and studies verified the diagnosis of muscle GSD0. He had a female sibling who died at 6 days of age of undetermined cause. Here we report the first muscle GSD0 patient in Asia with some distinct clinical manifestations from other reported cases.

2. Case report

An 11-year-old Japanese girl with repeated episodes of post-exercise loss of consciousness, weakness, and myalgia since age 5 years, was admitted to the hospital. She was the first child of unrelated healthy parents. She was born uneventfully and was normal in psychomotor development. At age 2 years, she developed the first episode of generalized tonic-clonic seizure while she was sleeping. At age 4 years, she had the second episode of generalized tonic-clonic seizure when she was under general anesthesia for tonsillectomy, whose cause was thought to be hypoglycemia due to prolonged fasting. In both episodes, seizure was followed by strong limb pain. At age 5 years, she suffered from the first episode of syncope while climbing up stairs. She recovered after a few hours. One year later, she had the second syncopal attack after running 50 m, which was accompanied by subsequent limb muscle weakness and myalgia. Since then, similar episodes were repeated several times a year. For each bout, she first developed leg muscle weakness immediately after exercise, making her squat down, and gradually lost the consciousness. She recovered her consciousness after a few hours but always experienced strong myalgia in legs which lasted for several hours. Blood glucose level was not decreased during these attacks.

On admission, general physical examination revealed no abnormal finding. On neurological examination, she had mild proximal dominant muscle weakness and mildly limited dorsiflexion of both ankle joints. T1-weighted images of skeletal muscle MRI showed high signal intensities in gluteal and flexor muscles of the thigh, which were assessed to be fatty degeneration (Fig. 1). Systemic investigations including electrocardiography, echocardiography, stress cardiac catheterization, stress myocardial scintigraphy, brain imaging, electroencephalography, and screening tests for metabolic diseases revealed no abnormality except for a mild ischemic finding on exercise electrocardiography. Ischemic and non-ischemic forearm exercise tests [8] showed the lack of lactate elevation, raising a possibility of glycogen storage disease. A few months later, resting electrocardiography, 24-h holter monitoring and resting echocardiography were re-evaluated and again revealed normal findings.

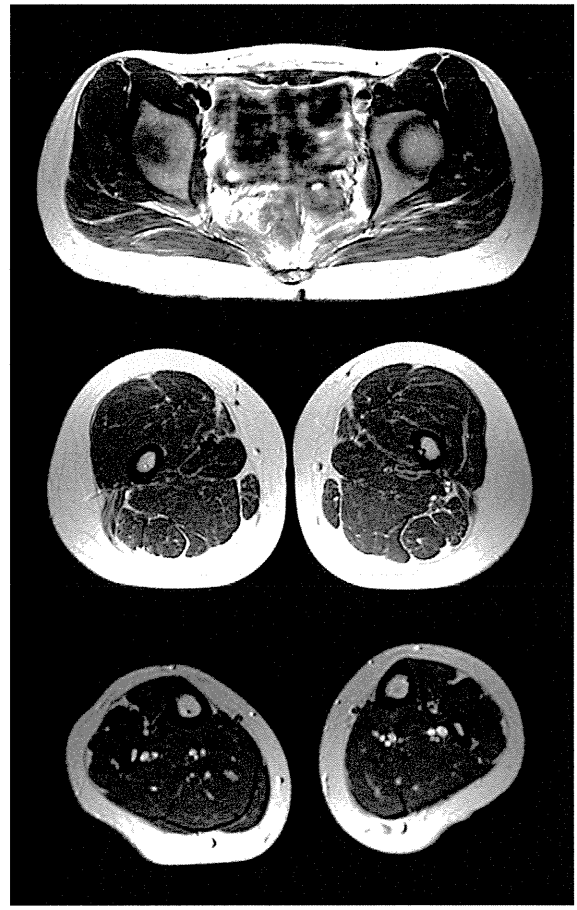

Fig. 1. Muscle MRI, T2WI, axial. It shows high intensity in gluteus maximus and biceps femoris muscles.

3. Histological analysis of skeletal muscle

Muscle biopsy was performed from biceps brachii. Serial frozen sections were stained with hematoxylin and eosin, modified Gomori trichrome, and a battery of histochemical methods. The most striking finding was depletion of glycogen in all muscle fibers but not in the interstitium on periodic acid-schiff (PAS) staining (Fig. 2A). Phosphorylase activity was also deficient in all fibers (Fig. 2B). Mitochondria especially at the periphery of muscle fibers were prominent on modified Gomori trichrome (Fig. 2D). ATPase staining revealed type 2 fiber atrophy. Electron microscopic analysis showed mitochondrial proliferation at the periphery of muscle fibers with no notable intramitochondrial inclusions (Fig. 2E).

4. Biochemical and molecular analysis

Both the activity of GYS1 and the amount of glycogen in the skeletal muscle were markedly reduced (Table 1). On western blotting, GYS1 in the patient's skeletal muscle was undetectable (Fig. 2F). The *GYS1* gene sequence analysis revealed compound heterozygous mutation of

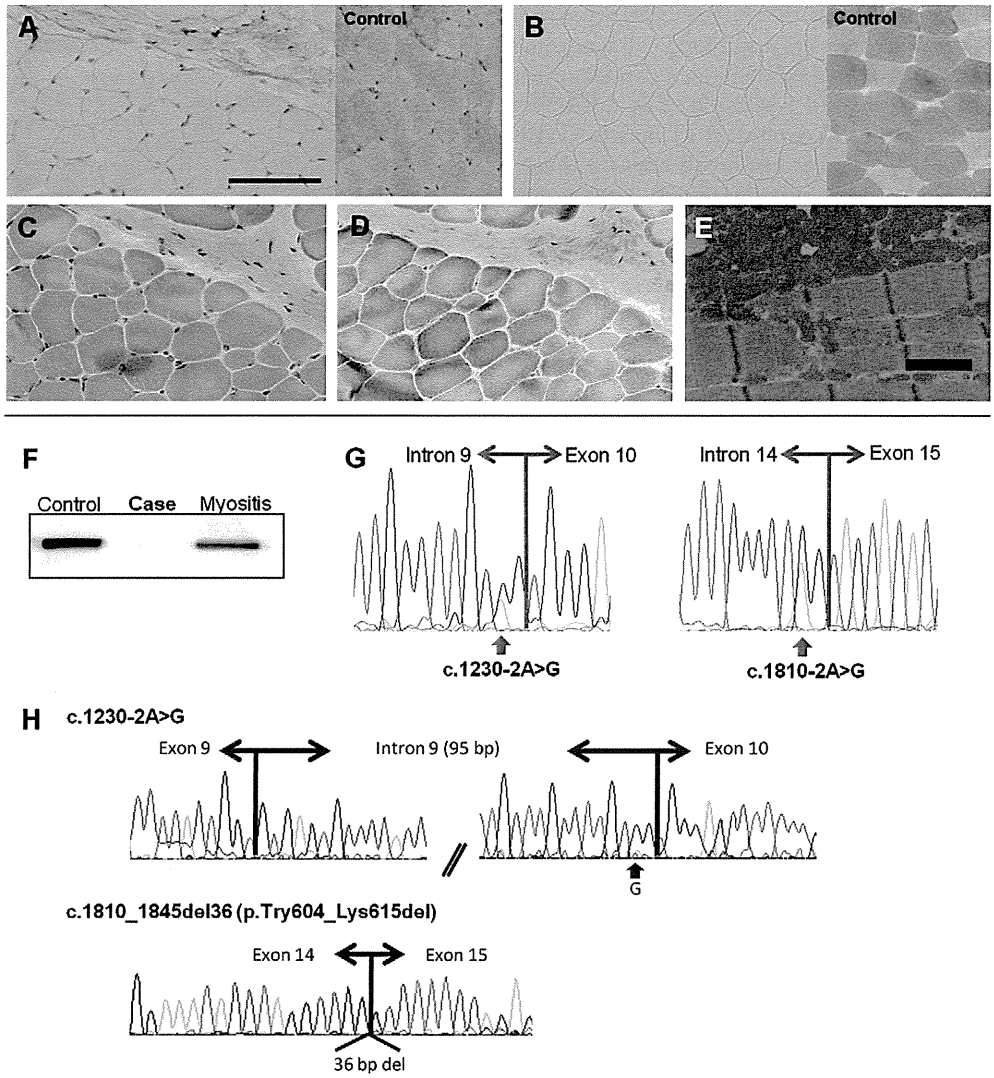

Fig. 2. Histological, genetic and protein analyses. Periodic acid-schiff (PAS) staining shows marked depletion of glycogen in muscle fibers but not in the interstitium (A). Phosphorylase activity is also deficient in all fibers (B). Hematoxylin and eosin staining shows mild fiber size variation (C). On modified Gomori trichrome, mitochondria are prominent especially at the margin of each muscle fiber (D). On electron microscopy (EM), mitochondria are increased in number at the periphery of muscle fibers (E). Bars represent 100 μm for histochemistry and 7 μm for EM. On western blotting using anti-GYS1 antibody (Abcam), GYS1 protein is absent in skeletal muscle from the patient (F). Sequence analysis for the *GYS1* gene reveals a compound heterozygous mutation of c.1230-2A > G and c.1810-2A > G (G). cDNA analysis showed insertion of intron 9 between exon 9 and 10 and 36-bp deletion from the beginning of exon 15 (H).

Table 1
Analyses of enzymatic activity and glycogen content. The activity of GYS and glycogen content in skeletal muscle were markedly reduced.

	Glycogen synthase (mol/min/mg)	UDPG-pyrophosphorylase (nmol/min/mg)	Glycogen contents (% of wet weight)
Patient	*0.9*	30.5	*0.03*
Control	42.0 ± 11.2	31.2 ± 3.5	0.94 ± 0.55

Italicized values: lower than control range.

c.1230-2A > G in intron 9 and c.1810-2A > G in intron 14 (Fig. 2G). cDNA analysis confirmed the insertion of the full-length intron 9 between exons 9 and 10 and a 36-bp deletion in the beginning of exon 15 (Fig. 2H).

5. Clinical course after diagnosis

Upon the diagnosis of GSD0, exercise was strictly limited to avoid syncope resulted from glucose depletion. In

addition, oral intake of cornstarch (2 g/kg, every 6 h) was started to maintain blood sugar level. Her condition had been stable for 1 year after diagnosis. However, at age 12 years, she was found lying unconsciously on the stairs at her school. She had persistent asystole despite ambulance resuscitation. The blood glucose level in the emergency room was above 100 mg/dl.

6. Discussion

We identified the first Asian patient with muscle GSD0, who manifested recurrent episodes of syncope with subsequent muscle weakness and myalgia, and eventually developed cardiac arrest.

Findings in our patient seem to be similar to previous reports, but some differences indicated the possibility of another pathogenesis of the disease. Our patient repeatedly suffered from episodes of syncope. In contrast to two earlier reports, those patients never had syncope, although the last attack led to sudden death [6,7]. In support of this notion, most muscle glycogen synthase knock-out mice died soon after birth due to impaired cardiac function [8]. However, the pattern of loss of consciousness in our patient cannot be explained by simple cardiac dysfunction, as she lost her consciousness gradually after exercise and took hours to regain, which is different from typical cardiac syncope, usually showing sudden loss of consciousness and rapid recovery. Alternatively, defective glycogen synthesis in brain may be related to syncope, as GYS1 is also expressed in brain, albeit not so much as in cardiac and skeletal muscles. Another possibility may be intermittent arrhythmia. However, electrocardiogram during the episode was never obtained. Further studies are necessary to answer this question.

On muscle pathology and electron microscopy, we found profound deficiency of glycogen in all muscle fibers accompanied by mitochondrial proliferation, which is similar to previous reports. The mitochondrial proliferation may reflect a compensatory mechanism for supplying ATP to glycogen-depleted muscles. Interestingly, phosphorylase activity on histochemistry seemed deficient. This is consistent with the fact that endogenous glycogen is used as a substrate of phosphorylase on histochemistry. Previous reports described the reduced number of type 2 fibers. In our patient, type 2 fiber atrophy, but not type 2 fiber deficiency, was seen. Although type 2 fiber atrophy is a nonspecific finding, this picture might also reflect the dysfunction of glycogen-dependent muscle fibers.

7. Conclusion

We identified the first Asian patient with muscle GSD0. In our patient, recurrent episodes of syncope and eventual sudden death may not be simply explained by cardiac dysfunction. Further studies are necessary to elucidate the mechanism of syncope in muscle GSD0 and to establish appropriate guideline of management for these patients to prevent sudden death.

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RESEARCH PAPER

Rapidly progressive scoliosis and respiratory deterioration in Ullrich congenital muscular dystrophy

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ABSTRACT

Objective To characterise the natural history of Ullrich congenital muscular dystrophy (UCMD).

Patients and methods Questionnaire-based nationwide survey to all 5442 certified paediatric and adult neurologists in Japan was conducted from October 2010 to February 2011. We enrolled the 33 patients (age at assessment, 11±6.6 years) who were reported to have collagen VI deficiency on immunohistochemistry in muscle biopsies. We analysed the development, clinical manifestations, Cobb angle and %vital capacity (%VC) in spirogram.

Results Cobb angle over 30° was noted at age 9.9 ±5.3 years (n=17). The maximum progression rate was 16.2±10°/year (n=13). %VC was decreased exponentially with age, resulting in severe respiratory dysfunction before pubescence. Scoliosis surgery was performed in 3 patients at ages 5 years, 9 years and 10 years. Postoperative %VC was relatively well maintained in the youngest patient. Non-invasive ventilation was initiated at age 11.2±3.6 years (n=13). Twenty-five (81%) of 31 patients walked independently by age 1.7±0.5 years but lost this ability by age 8.8 ±2.9 years (n=11). Six patients never walked independently.

Conclusions The natural history of scoliosis, respiratory function and walking ability in UCMD patients were characterised. Although the age of onset varied, scoliosis, as well as restrictive respiratory dysfunction, progressed rapidly within years, once they appeared.

INTRODUCTION

Ullrich congenital muscular dystrophy (UCMD) is, after Fukuyama CMD, the second most common CMD in Japan.[1] UCMD is characterised by proximal joint contractures, distal joint hyperlaxity, proximal muscle weakness, scoliosis and respiratory failure.[1–4] The prevalence of UCMD is reported to be 1.3 per million in northern England.[5] Mutations in either *COL6A1*, *COL6A2* or *COL6A3* gene, each encoding a subunit of collagen VI (COL6), are known to cause UCMD. We have previously shown that there are two modes of COL6 deficiency: complete COL6 deficiency (CD) and sarcolemma specific COL6 deficiency (SSCD),[6 7] which are associated with recessive and de novo dominant mutations in *COL6* genes, respectively.[1]

To date, there is no cure for UCMD, and patients rely on supportive treatment of symptoms such as spinal deformity and respiratory failure. However, pathological hypotheses leading to myofibre degeneration in COL6-deficient skeletal muscle have been proposed and therapeutic targets have been suggested.[8] There is currently a clinical trial for UCMD patients based upon the theory of impaired autophagy.[9 10] Furthermore, a gene-based therapy to inhibit mutant transcripts by antisense has also been proposed because an abnormal mutated subunit can be assembled into growing supramolecular structures and sequester normal subunits into non-functional complexes, thus exerting dominant-negative effect.[11 12] Advances in such therapeutic research make knowledge of the natural course of the disease and appropriate outcome measures necessary. However, only limited information is available, especially regarding the rate of disease progression.[13] We have therefore attempted to determine the natural history of UCMD.

PATIENTS AND METHODS

This clinical study was performed in conformity with the Declaration of Helsinki for investigation involving human subjects and was approved by the ethics committee of the National Center of Neurology and Psychiatry.

A questionnaire-based nationwide survey was conducted from October 2010 to February 2011. The questionnaire was mailed to all 5442 certified paediatric and adult neurologists by the Japanese Society of Child Neurology and the Japanese Society of Neurology, and we received 1881 (34.6%) responses. This survey consisted of questions about perinatal and developmental aspects, age and clinical manifestations at diagnosis, age at assessment, age at loss of ambulation, age at scoliosis surgery, age at initiation of non-invasive ventilation (NIV), data of Cobb angle on x-ray and % vital capacity (VC) in spirogram, in addition to pathological findings and COL6 immunohistochemistry in biopsied muscle (table 1).

Among 40 patients reported to have UCMD, we enrolled 33 patients (15 men and 18 women) with COL6 deficiency: 5 with CD and 28 with SSCD, on immunohistochemistry in skeletal muscle. Sequence analysis of *COL6* genes was performed using genomic DNA from 32 patients, 19 (59.4%) of whom carried identifiable mutations (table 2). All the 14 patients, who were not genetically confirmed, manifested clinical features compatible with UCMD in addition to COL6 deficiency (tables 2 and 3).[14] Age at muscle biopsy was 3.2±2 years

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Table 1 Summary of questionnaire items in this study

Items		Items	
Patient's visit	**Yes/No**	**Age at muscle biopsy**	**Age**
Age at assessment	Age	Clinical manifestation at diagnosis	
Sex	Male/Female	Distal joint hyperlaxity	Yes/No
Muscle biopsy	Yes/No	Protruding calcaneus	Yes/No
COL6 deficiency on IHC	Yes/No	High arched palate	Yes/No
Mode of COL6 deficiency	CD/SSCD	Proximal joint contractures	Yes/No
Perinatal history		Scoliosis	Yes/No
Decreased fetal movement	Yes/No	Spinal rigidity	Yes/No
Poor sucking	Yes/No	Ankle joint contracture	Yes/No
Floppiness	Yes/No	Facial weakness	Yes/No
CHD	Yes/No	Skin lesions	Yes/No
Torticollis	Yes/No		
AMC	Yes/No	Age at loss of ambulation	Age
Developmental history		NIV	Yes/No
Head control	Age	Age at initiation of NIV	Age
Sitting	Age	Data of %VC	
Walking	Age	Age at scoliosis surgery	Age
Phrases	Age	Data of Cobb angle	

AMC, arthrogryposis multiplex congenita; CD, complete collagen VI deficiency; CHD, congenital hip dislocation; COL6, collagen VI; IHC, immunohistochemistry; NIV, non-invasive ventilation; SSCD, sarcolemma-specific collagen VI deficiency; VC, vital capacity.

(mean±SD). Age at assessment was 11±6.6 years. We analysed the information on perinatal abnormalities, development, clinical features, deterioration of ability to walk, progression of scoliosis and respiratory dysfunction.

RESULTS

Perinatal abnormalities and clinical manifestations are shown in tables 2 and 3. Congenital hip dislocation, torticollis and arthrogryposis multiplex were noted in 36.4%, 27.3% and 20% of patients, respectively. More than 50% of patients had distal joint hyperlaxity, protruding calcaneus, high arched palate, proximal joint contractures and scoliosis. Creatine kinase level at muscle biopsy was 315±110 IU/L (n=31). Among patients with CD, homozygous or compound heterozygous mutations were identified in three but a heterozygous mutation was identified in one patient. All the 15 patients with SSCD carried a heterozygous mutation (table 2).

Twenty-five (81%) of 31 patients were able to sit and walk independently. Six patients (19%) never walked, three of whom had CD by muscle immunohistochemistry (tables 2 and 3). Head control, sitting and independent ambulation were completed at median ages of 4 months, 9 months and 18 months, respectively (figure 1A). In contrast, achievement of speaking phrases was not delayed, ranging from ages 12 months to 25 months (figure 1A). Most patients became able to walk independently by age 2 years but this ability deteriorated with age (figure 1B). Loss of ambulation occurred at age 8.8±2.9 years (n=11). Patient 18 was reported to walk with knee-ankle-foot orthoses at age 11 years. Patients 20 and 30, respectively, required a wheelchair at ages 13 years and 6 years. Half of the patients became wheelchair-bound by age 11 years (figure 1B). Six patients became wheelchair-bound by age 7 years, two of whom had CD and loss of ambulation at ages 5.5 years and 6 years, respectively. Two of four patients with SSCD who carried a heterozygous c.850G>A (p.Gly284Arg) mutation in *COL6A1* did not acquire independent ambulation (tables 2 and 3).

The severity and progression of scoliosis were assessed by Cobb angle (n=23). Maximum Cobb angles are shown in table 3. Patient 28 was reported to suffer from marked scoliosis albeit no data of Cobb angle was available. Cobb angle over 30° was noted at age 9.9±5.3 years in 17 patients (table 4). Among them 13 patients had Cobb angle data available for 3 or more years and show a maximum progression rate of 16.2±10°/year. Overall, although the onset of scoliosis varied, it progressed rapidly within years once scoliosis was noted (figure 1C). Surgical intervention for scoliosis was performed in Patients 8, 9 and 21 at ages 10 years, 9 years and 5 years, respectively. Presurgical and postsurgical Cobb angle data were available in the last two patients, both of whom showed improvement from 107° to 80° and 90° to 40°, respectively.

Percent VCs at survey are shown in table 3. Patients 8 and 27 had 32% and 70.4% of predicted VC at ages 8 years and 6 years, respectively. Respiratory function, measured by %VC (n=20), decreased exponentially with age accompanied by a sharp decline below age 10 years (figure 1D). Importantly, postoperative VC was relatively well maintained in the patient who underwent surgery at age 5 years (figure 1D). The percentage of patients requiring NIV increased with age (figure 1E). Half of the patients required NIV by age 12 years. Age at initiation of NIV was 11.2±3.6 years (n=13) (table 3). On the other hand, %VC at mean age of NIV initiation was estimated at around 36%.

DISCUSSION

This is the first nationwide survey of the natural history of UCMD in Japan. This study confirmed the previously reported clinical features of UCMD: delayed motor milestone, absence of mental retardation, distal joint hyperlaxity, proximal joint contractures, scoliosis and respiratory involvement.[1–4] Furthermore, we characterised the natural history of scoliosis, respiratory function and ambulation in this relatively large UCMD series.

UCMD is on a disease spectrum of COL6 related myopathy. Intermediate phenotypes, named mild UCMD or severe Bethlem myopathy, have been known, and currently there is no

Table 2 Clinical, pathological and genetical findings in the 33 patients

Pt	Age at biopsy (years)	Clinical manifestations and CK level at muscle biopsy										Collagen VI	
		Distal joint hyperlaxity	Protruding calcaneus	High arched palate	Proximal joint contracture	Scoliosis	Spinal rigidity	Ankle joint contracture	Facial weakness	Skin lesion	CK	Deficiency on IHC	Gene mutation
1	3	(+)	ND	(+)	(–)	ND	ND	(–)	(+)	(–)	440	CD	*COL6A2* c.1771-3G>C *COL6A2* c.1270-1G>C
2	2	(+)	(+)	(–)	(+)	(+)	(–)	(–)	(–)	(+)	413	CD	*COL6A3* c.5692delG p.Val1898fs *COL6A3* c.8737delG p.Ala2913fs
3	2	(+)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	(+)	474	CD	NF
4	1	ND	(+)	(–)	(–)	(–)	(–)	(–)	(+)	(–)	339	CD	*COL6A2* c.2678_2700del23 p.Pro893fs homozygous
5	1	ND	(+)	(–)	(+)	ND	(+)	(+)	(+)	(–)	ND	CD	*COL6A3* c.4184G>A p.Arg1395Gln
6	2	(+)	(+)	(+)	(–)	ND	ND	(–)	(–)	(–)	290	SSCD	*COL6A1* c.850G>A p.Gly284Arg
7	1	(+)	ND	(+)	(+)	(+)	(+)	(+)	(–)	ND	195	SSCD	*COL6A1* c.850G>A p.Gly284Arg
8	1	(+)	(+)	ND	(+)	ND	(+)	(+)	ND	(–)	319	SSCD	NF
9	3	(+)	(–)	ND	(+)	(+)	ND	(–)	ND	(–)	ND	SSCD	NF
10	3	(+)	(+)	(+)	(+)	(+)	(–)	(–)	(–)	(+)	428	SSCD	*COL6A2* c.950_954+8del
11	5	(+)	(+)	(+)	(+)	(+)	(+)	(–)	(–)	(–)	151	SSCD	NA
12	4	(+)	(+)	(–)	(+)	(+)	ND	(–)	(–)	ND	207	SSCD	*COL6A2* c.901G>T p.Gly301Cys
13	6	ND	(–)	(+)	(–)	(–)	(–)	(+)	(–)	(–)	564	SSCD	NF
14	7	(–)	(+)	(+)	(–)	(–)	(–)	(–)	(–)	(–)	329	SSCD	*COL6A2* c.812G>A p.Gly271Asp
15	5	(+)	(–)	(+)	(–)	(+)	(–)	(–)	(+)	(–)	289	SSCD	*COL6A1* c.958_966del9 p.Gly320_Lys322del
16	3	(–)	ND	(+)	(–)	(–)	(–)	(–)	(–)	(–)	425	SSCD	*COL6A3* c.6210+2T>A
17	3	ND	ND	(+)	ND	ND	ND	ND	(–)	ND	242	SSCD	*COL6A1* c.850G>A p.Gly284Arg
18	2	(+)	(+)	(+)	(+)	(–)	(+)	(+)	(+)	(–)	299	SSCD	NF
19	3	(–)	(+)	(+)	(+)	(–)	(–)	(+)	(–)	(–)	464	SSCD	NF
20	1	ND	ND	(+)	(–)	(–)	(–)	(–)	(–)	ND	254	SSCD	*COL6A1* c.958_966del9 p.Gly320_Lys322del
21	5	(+)	ND	(–)	(–)	(+)	(+)	(–)	(–)	(–)	138	SSCD	*COL6A1* c.868G>A p.Gly290Arg
22	6	(+)	ND	(–)	(+)	(–)	(–)	(+)	(–)	(–)	495	SSCD	NF
23	1	(+)	(+)	(+)	(+)	(–)	(–)	(–)	(–)	(+)	300	SSCD	*COL6A1* c.850G>A p.Gly284Arg
24	2	(+)	(+)	(+)	(+)	(–)	(–)	(–)	(+)	(–)	388	SSCD	NF
25	4	(+)	(+)	(–)	(–)	(+)	(+)	(–)	(–)	(–)	277	SSCD	*COL6A1* c.860G>A p.Gly287Glu
26	6	(+)	(+)	(+)	(–)	(+)	(+)	(+)	(–)	(–)	103	SSCD	NF
27	5	ND	ND	ND	ND	ND	ND	ND	ND	ND	262	SSCD	*COL6A1* c.1056+1G>A
28	8	ND	(–)	(+)	(+)	ND	(+)	(–)	(+)	(+)	254	SSCD	NF
29	2	ND	ND	(–)	(–)	(+)	(–)	(–)	(–)	(–)	361	SSCD	*COL6A3* c.6210+1G>A
30	3	(–)	(+)	ND	(–)	(–)	(–)	(–)	ND	(–)	278	SSCD	*COL6A3* c.6310-2A>G
31	1	(+)	ND	(–)	(+)	(+)	(–)	(–)	(–)	(–)	261	SSCD	NF
32	4	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(–)	(–)	323	SSCD	NF
33	0	(+)	(–)	(+)	(+)	(+)	(+)	(–)	(–)	(–)	214	SSCD	NF
		21/25 (84%)	18/23 (78.3%)	19/29 (65.5%)	17/31 (54.3%)	14/ 26 (53.8%)	11/ 27 (40.7%)	9/31 (29%)	7/29 (24.1%)	5/ 28 (17.9%)			

CD, complete deficiency; CK, creatine kinase; IHC, immunohistochemistry; NA, not available; ND, no data; NF, not found; Pt, patient; SSCD, sarcolemma specific collagen VI deficiency; (+); present, (–); absent.

Table 3 Perinatal, developmental history and disease progression in our series

		Perinatal history						Developmental milestone (months)				Motor function at survey		Respiratory function			
Pt	Age at survey (years)	Floppiness	Poor sucking	CHD	Decreased fetal movement	Torticollis	AMC	Head control	Sit	Walk	Phrases	Walk independently	Age at loss of ambulation (yrs)	%VC at survey (%)	NIV	Age at initiation of NIV (yrs)	Maximum Cobb angle (°) (yrs)
1	14	(+)	(+)	(+)	(+)	(+)	(+)	6	30	(–)	ND	(–)		29	(+)	8	45 (11)
2	10	(–)	(+)	(+)	(–)	(–)	ND	5	12	(–)	ND	(–)		22.3	(+)	8	12 (10)
3	7	(+)	(–)	(+)	(–)	(+)	(–)	ND	9	24	24	(–)	5.5	55	(–)		ND
4	3	(–)	(+)	(–)	(–)	(+)	(–)	7	12	(–)	25	(–)		ND	(–)		0 (3)
5	23	(+)	(+)	(+)	(–)	(–)	(–)	ND	ND	18	ND	(–)	6	14.9	(+)	15	50 (23)
6	23	(+)	(+)	(+)	(+)	(+)	(–)	5	18	(–)	18	(–)		10.4	(+)	15	54 (23)
7	14	(+)	(+)	(+)	(–)	(+)	(–)	3	11	(–)	23	(–)		ND	(+)	5	99 (9)
8	21	(–)	(–)	(–)	(–)	(–)	ND	5	12	(–)	ND	(–)		ND	(+)	9	53 (10)
9	20	ND	ND	(–)	ND	(+)	(–)	4	7	18	16	(–)	6	12.2	(+)	10	107 (9)
10	6	(–)	(–)	(+)	(–)	(–)	(–)	3	12	24	18	(–)	6	ND	(–)		20 (6)
11	10	(–)	(–)	(–)	(+)	(–)	(–)	3	7	18	19	(–)	7	46	(–)		10 (10)
12	15	(+)	(–)	(–)	(–)	(–)	(–)	4	8	22	24	(–)	10	37.9	(–)		31 (3)
13	15	(–)	(–)	(+)	(–)	(–)	ND	5	6	18	18	(–)	10	27.6	(+)	12	60 (15)
14	15	(+)	(–)	(+)	(+)	(–)	(–)	5	12	16	12	(–)	11	15.7	(+)	9.5	110 (15)
15	13	(+)	(+)	(–)	(+)	(–)	(–)	4	7	14	24	(–)	11	21.9	(+)	11	94 (14)
16	11	(–)	(+)	(–)	(–)	(–)	(+)	4	6	16	16	(–)	11	30.7	(–)		70 (11)
17	23	(–)	(+)	(–)	(–)	(–)	(–)	4	8	16	24	(–)	14	19.8	(+)	16	41 (23)
18	10	(+)	(+)	(–)	(+)	(–)	(–)	7	9	27	24	(+)		45	(–)		0(9)
19	3	(–)	(–)	(–)	(–)	(–)	(–)	8	11	24	24	(+)		ND	(–)		ND
20	16	(+)	(–)	(–)	(–)	(–)	(+)	4	8	20	12	(+)		ND	(+)	10	90(10)
21	12	(–)	(–)	(+)	(–)	(–)	(–)	6	15	30	14	(+)		44.3	(–)		90(5)
22	10	(–)	(–)	(–)	(+)	(–)	(–)	4	8	14	24	(+)		58.9	(–)		0(10)
23	5	(+)	(–)	(–)	(–)	(–)	(–)	2	7	14	21	(+)		ND	(–)		2(4)
24	5	(–)	(–)	(+)	ND	(–)	(–)	3	8	22	18	(+)		ND	(–)		5(5)
25	5	(–)	(+)	(–)	(–)	(+)	ND	4	6	15	ND	(+)		ND	(–)		60(6)
26	7	(+)	(+)	(–)	(+)	(–)	(+)	3	12	24	18	(+)		53.4	(–)		46(7)
27	11	(–)	(–)	(–)	ND	(–)	ND	4	8	16	ND	ND		ND	(–)		ND
28	18	(+)	(+)	(–)	(+)	(–)	ND	ND	20	36	24	(+)		ND	(+)	17	ND
29	2	(+)	(–)	(–)	ND	(+)	(–)	4	8	19	ND	(+)		ND	ND		ND
30	7	(–)	(–)	(–)	(–)	(–)	ND	3	8	13	24	(+)		ND	(–)		ND
31	1	(–)	(–)	(–)	(+)	(–)	(+)	6	14	ND	ND	ND		ND	ND		ND
32	6	(–)	(–)	(–)	(–)	(–)	ND	5	9	18	22	(+)		ND	(–)		40(4)
33	1	(+)	(–)	(+)	(–)	(+)	(–)	7	(–)	ND	ND	ND		ND	(–)		5(1)
		15/32 (46.9%)	13/32 (40.6%)	12/33 (36.4%)	10/29 (34.5%)	9/33 (27.3%)	5/25 (20%)										

Pt 18 was reported to walk with knee-ankle-foot orthoses at age 11 years. Pts 20 and 30 were reported to be able to walk independently but they respectively required a wheelchair at ages 13 years and 6 years. Pts 8 and 27 showed 32% and 70.4% of predicted VC at ages 8 years and 6 years, respectively. Pt 28 was reported to suffer from marked scoliosis but no data of Cobb angle was available.
AMC, arthrogryposis multiplex congenita; CHD, congenital hip dislocation; ND, no data; NIV, noninvasive ventilation; Pt, patient; %VC, % vital capacity; (+), present; (–), absent.