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A JAPANESE CMD CASE WITH DIFFUSE WHITE MATTER HYPERLUCENCY ON CT AND NORMAL MENTALITY: A 16 YEAR FOLLOW-UP STUDY

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A 22y7m old male with non-Fukuyama type congenital muscular dystrophy (non-FCMD), suffering from profound muscle weakness, pes equinovarus since early infancy, with entirely normal mentality despite diffuse white matter hyperlucency on computed tomography without ventricular dilatation, who had been examined at four and 20 years of age with essentially no change during the 16 year interval, is reported. Congenital muscular dystrophy was diagnosed at 8m based on an elevated serum creatine kinase (CK) value and the results of electromyography and muscle biopsy. He never became ambulant but did attain head control, the ability to maintain a sitting posture and sliding on his buttocks. Maximum motor ability was maintained until age 11y. Involvement of the facial musculature and multiple joint contractures developed. He experienced convulsions induced by a fever. Leukocyte lysosomal enzymes were all within normal limits. Cerebrospinal fluid was negative for demyelinating antibodies. Motor nerve conduction velocities examined at 4y2m were within normal limits. Genetic analysis of the FCMD gene locus revealed the patient to have the same haplotype, in terms of the centromere side of mfd220, as one of his healthy elder brothers with normal CK values.

In addition, we have reviewed the literature on non-FCMD with similar findings and present two other similar cases in our experience.

Introduction

In 1977, at the 19th Annual Meeting of the Japanese Child Neurology Society[1], and in 1979, at the 2nd Congress of the International Child Neurology Society held in Sydney, Australia[2], we reported the striking brain computed tomographic (CT) finding of a diffuse low density area in the white matter (WM) of a four year old boy with congenital muscular dystrophy (CMD) and entirely normal mentality. He had marked hypotonia which had been present since early infancy. A diffuse hyperlucent area was identified in the WM on CT scan. We classified this case as CMD II (non-Fukuyama type congenital muscular dystrophy; non-FCMD), in a report published in 1981, based on his normal intelligence[3]. Similar cases have subsequently been reported in western countries[4)~22)] and also in Japan[23)~26)]. Sixteen years later we had a chance to re-examine the brain CT in this case and confirmed the findings to be essentially unchanged. We believe that this case merits documentation and the

findings are described herein.

In addition, we have reviewed the literature on non-FCMD with similar findings[4)~26)], i.e. "pure" CMD with normal mentality and WM hyperlucency on CT, and present two other similar cases in our experience. The salient features of the three cases described herein include muscular weakness present since birth, delayed motor developmental milestones, hypotonia, muscle atrophy, involvement of the facial musculature, areflexia, multiple joint contractures and some dysmorphic features such as high-arched palate, a thin elongated face, macrocephaly, and abnormalities of jaw articulations. The intelligence quotient (IQ) is essentially normal or only very slightly subnormal. Some patients have epileptic seizures, others do not. Marked WM hyperlucency is evident on CT scan.

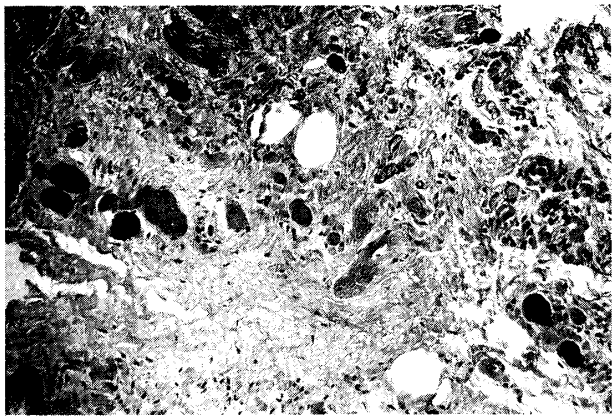

Fig. 1 Quadriceps femoris muscle biopsy obtained at 8m old
The Masson-Trichrome stained specimen, magnified 100×, reveals loss of basic muscle architecture, with replacement by fatty and connective tissues which have infiltrated the endomysium and perimysium, occasional small rounded muscle fibers and, rarely, hypertrophic or degenerative fibers.

Case Presentation

The patient reported in 1981[3)] is now 22y7m old and suffers from profound muscle weakness. There is no family history of either neuromuscular disease or a convulsive disorder, the parental marriage is nonconsanguineous and both elder brothers are healthy. His father was 37 and his mother 31 at the time of his birth. His parents and brothers have normal creatine kinase (CK) values and no indications of muscle weakness.

The mother reported an uneventful pregnancy. The patient had been born at 39 weeks gestation, weighing 3,300 g. Pes equinovarus had been noted on physical examination at 1m of age. Orthopedic shoes had been prescribed at 3m and were worn for one month. He had been able to follow an object at 2m, to smile at 3m and started to develop a vocabulary at 10m. His mother consulted a pediatrician when he was 5m old as the patient had not yet attained head control. CMD was diagnosed at 8m based on an elevated serum CK value and the results of electromyography (EMG) and muscle biopsy (Fig. 1). He subsequently attained head control, at 9m, and the ability to maintain a sitting posture, at 10m, and was able to roll over by 1y10m. He experienced two convulsions, induced by a fever of more than 38°C while suffering from the mumps, at 2y of age.

He was initially brought to our hospital at 2y5m (Fig. 2). His head circumference was 52.0 cm (48.9 ± 1.7 cm, +1.8SD), body weight 12.0 kg (12.3 ± 1.3 kg, −0.2SD) and chest circumference 48.0 cm (normal average: 50.1 cm). His stature and build were within normal range but his head was relatively large. The head shape was brachycephalic with a mild plagiocephaly. He was very cooperative during the physical examination and his mentality was found to be normal. Generalized but proximal dominant muscle weakness, most evident in the upper extremities, and hypotonia were observed. Cranial nerve examination revealed dysfunction of the muscles innervated by cranial nerve V, with weak pterygoid and masseter muscles, and his family had noticed weak biting and chewing. Facial muscles innervated by cranial nerve VII showed mild weakness, especially of the orbicularis oris and oculi. He was able to close his eyes and mouth, but rather weakly. Dysfunction of the muscles innervated by cranial nerves IX

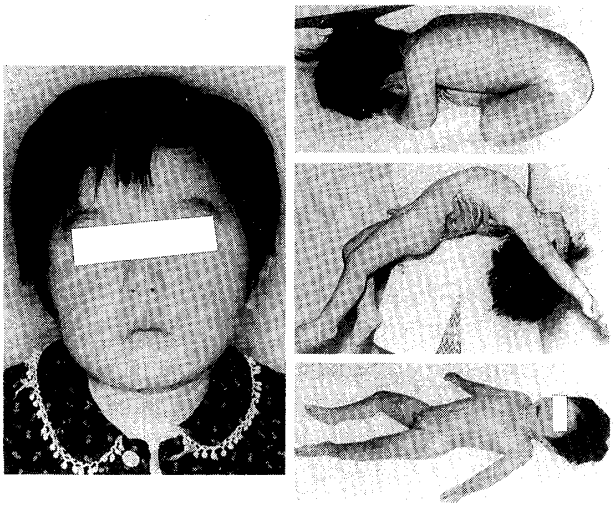

Fig. 2 Clinical features at age 2y6m
Marked hypotonia is evidenced by double folding, complete absence of anti-gravity movements when held horizontally and frog posture while supine. At this stage, facial involvement is, however, mild and the patient is able to close his mouth. This patient's above average intelligence is reflected in the alert expression on his face and in his eyes.

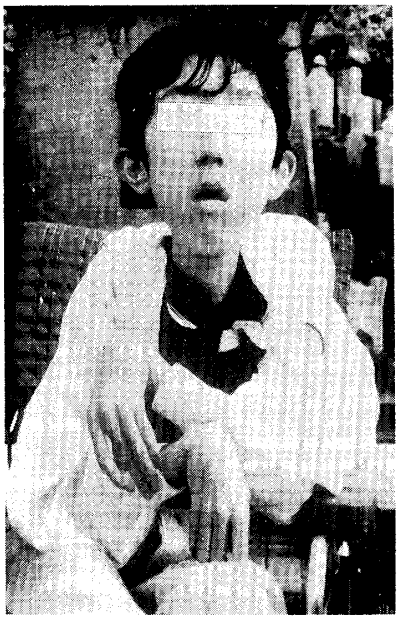

Fig. 3 Clinical features at age 19y
By age 19y thinning and elongation of the face with buccal atrophy, a sharp chin and shallow nasolabial folds have appeared. The patient is no longer able to close his mouth. Joint contractures of the wrists are severe while those of the finger joints are comparatively mild.
He can maintain a sitting position while in a wheelchair but his posture is severely compromised due to trunk muscle weakness and marked scoliosis.

and X manifested as a small voice volume, poor cough and weak gag reflex. Dysfunction of the muscles innervated by cranial nerve XI produced head lag. No atrophy of the tongue or decreased tongue mobility was noticed. He was able to raise his upper extremities approximately 120° against gravity but loose shoulder joints and winged scapulae were noted. He also showed lumbar lordosis while sitting. Deep tendon reflexes were negative. There was no evidence of pseudohypertrophy. Pes equinovarus, limited knee extension and heel protrusion were recognized. He also had undescended testes.

This patient never became ambulant but was able to maintain a standing posture while in a deep bath tub, partially due to the presence of water, by holding the edge of the tub. He began sliding on his buttocks at 2y6m and maintained this ability until age 11y. At age 19y (Fig. 3), marked thinning of the face, multiple joint contractures, and scoliosis had become evident, but he was able maintain a sitting postute while in a wheelchair. He completed elementary education, as well as junior and senior high school, and his academic performance was good throughout. At present, he continues to enjoy using a word processor, drawing and playing Shougi (an intellectually challenging game comparable to chess). He is still able to sit in a wheelchair though his posture is severely comprised while doing so. Neither respiratory insufficiency nor cardiac muscle involvement has

Table 1 Leukocyte glycosidase activity

Enzyme		Patient	Normal value nmole/mg/hr
N-Acetyl-β-glucosaminidase	Total	930.2	380～800
	Hex A%	57.9	40～ 60
Arylsulphatase A		53.5	40～110
4-MU-β-galactosidase		227.0	80～300
Galactocerebrosidase		0.94	0.5～2.7

developed to date.

Laboratory data, obtained in early childhood, included a CK level of 935 mU/ml (normal range<100 mU/ml). CK isozymes were MM 90%, MB 4% and BB 0%. At age 6y, his CK level was 407 mU/ml, four times the upper limit of normal. Leukocyte lysosomal enzymes (acetyl-β-glucosaminidase, arylsulfatase A, 4-MU-β-galactosidase) were all within normal limits (Table 1). Cerebrospinal fluid was negative for demyelinating antibodies. His IQ was 117 at 2y5m. Motor nerve conduction velocities examined at 4y2m were within normal limits: N. ulnar 53.7 m/sec, N. medianus 48.6 m/sec, N. peroneal 46.0 m/sec. Sensory nerve conduction velocity was 60.4 m/sec. Diffuse hyperlucency in the WM, without ventricular dilatation, was revealed by CT at age 4y (Fig. 4). These findings were unchanged at 20y (Fig. 5). The most recent CK value, obtained at 22y7m, was 148 mU/ml (a normal level at the institution at which the measurement was done). This normal CK value reflects widespread loss of muscle tissue. Blood gases obtained at the same time were normal.

Genotyping

Genetic analysis of the Fukuyama type congenital muscular dystrophy (FCMD) gene locus was conducted for this patient, his parents and his two healthy elder brothers.

We used nine polymorphic microsatellite CA repeat markers, previously described as being on chromosome 9[27)~30)]. The markers used were D9S176[30)], D9S109[31)], D9S127[32)], mfd220[33)], CA246[34)], D9S58[35)], D9S105[36)], D9S59[36)] and HXB[37)]. The FCMD gene is considered to lie within a few hundred kilobases of the mfd220 locus[34)].

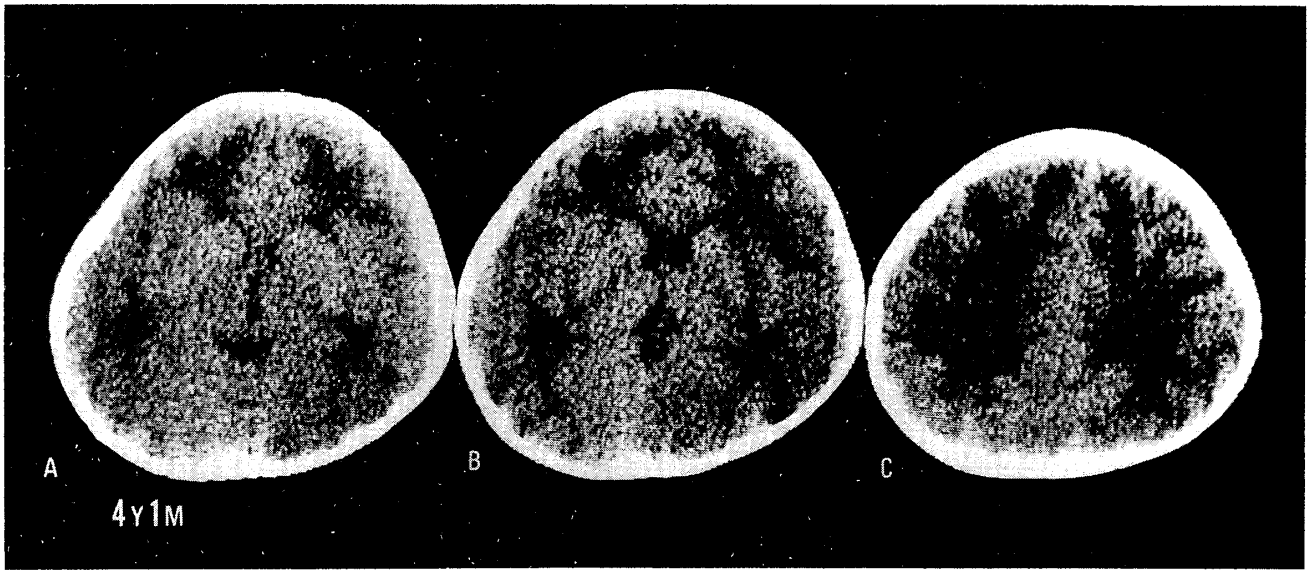

Fig. 4 Computed tomography at 4ylm old

Diffuse and marked white matter hyperlucency, without dilatation of the ventricles or the subarachnoid space, was seen. The EMI number in the subfrontal white matter was calculated to be 9.9 ± 2.09, lower than the average of age-matched controls, 15.3 ± 0.6. The EMI number in the caudate nucleus, calculated as a representative gray matter area, was 19.7 ± 2.6, comparable to the age-matched normal control average of 17.9 ± 0.7.

A: CT obtained at the level of the foramen of Monro and quadrigeminal cistern. Diffuse marked hyperlucency of white matter in the frontal and temporal lobes was observed symmetrically without dilatation of the anterior horn, third ventricle or Sylvian fissure.

B: CT at pineal body level. Diffuse and marked white matter hyperlucency is evident in the frontal, temporal and occipital lobes.

C: CT obtained above the corpus callusum level. Diffuse and marked white matter hyperlucency is apparent at the centrum semiovale.

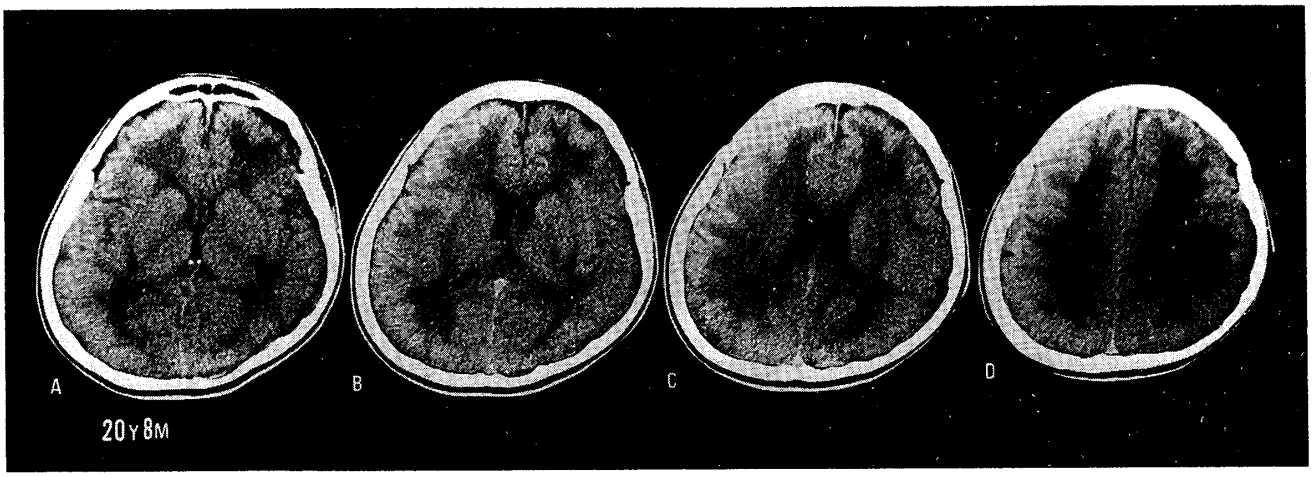

Fig. 5 Computed tomography at 20y8m old
Diffuse and marked white matter hyperlucency, whithout dilation of the ventricles or the subarachnoid space, was essentially unchanged as compared to the CT images obtained at 4y1m. As a consequence of plagiocephaly, the hyperlucency area appears to be wider on the left in some images (B, C) and on the right in others (D).
A: CT at pineal body level. Diffuse and marked white matter hyperlucency can be seen in the frontal, temporal and occipital lobes, in the posterior limb of the internal capsule, in the capsula externa and extrema.
B: CT at the splenium level. The anterior horns, trigonum and posterior horns of the lateral ventricles do not appear dilated. Diffuse hyperlucency is evident in the anterior, parietal and occipital lobes, as well as the capsula externa and extrema.
C: CT at subcorpus callosum level. Diffuse hyperlucency is apparent in the white matter of both the frontal and the occipital lobe. No evidence of cortical dysplasia was detected.
D: CT obtained above the corpus callosum level. Diffuse and marked white matter hyperlucency can be seen at the centrum semiovale.

Polymerase chain reaction (PCR) and electrophoresis conditions were as previously described[34)38)]. To reveal simple sequence repeat polymorphisms, 20 ng of genomic DNA from each subject was amplified by PCR using 20 pmol of each primer in 25 μl of reaction buffer. Samples were incubated in a DNA thermocycler (Perkin Elmer Cetus) for 35 cycles under the following conditions: 94°C for 2 min, 55°C for 3 min and 72°C for 2 min. After PCR, the products were analyzed on 6% polyacrylamide gels, and visualized by autoradiography.

Polymorphism analysis

Based on the genotypic data, haplotypes were identified (Fig. 6). The patient was found to have the same haplotype, in terms of the centromere side of mfd220, as one of his elder brothers. This would be highly unlikely if his diagnosis were FCMD. The findings obtained by genetic analysis not only confirm that this patient does not have FCMD, but also indicate that the gene responsible for this disorder is at a different locus.

Additional Cases

At the Department of Pediatrics of Tokyo Women's Medical College Hospital, we have experienced only three cases of CMD with normal mentality and elevation of serum CK. All three had been floppy since early infancy. In contrast we followed 83 cases of typical FCMD and 14 of benign FCMD during the 1972 to 1993 period. The other two of our CMD cases with normal mentality, appear to belong the same category even though they were not examined by CT. There clinical data are shown in Table 2. Both girls were symptomatic before 3m of age and head control was delayed until 7m of age in one case and 11m in the other. Both were able to maintain a sitting posture within a few

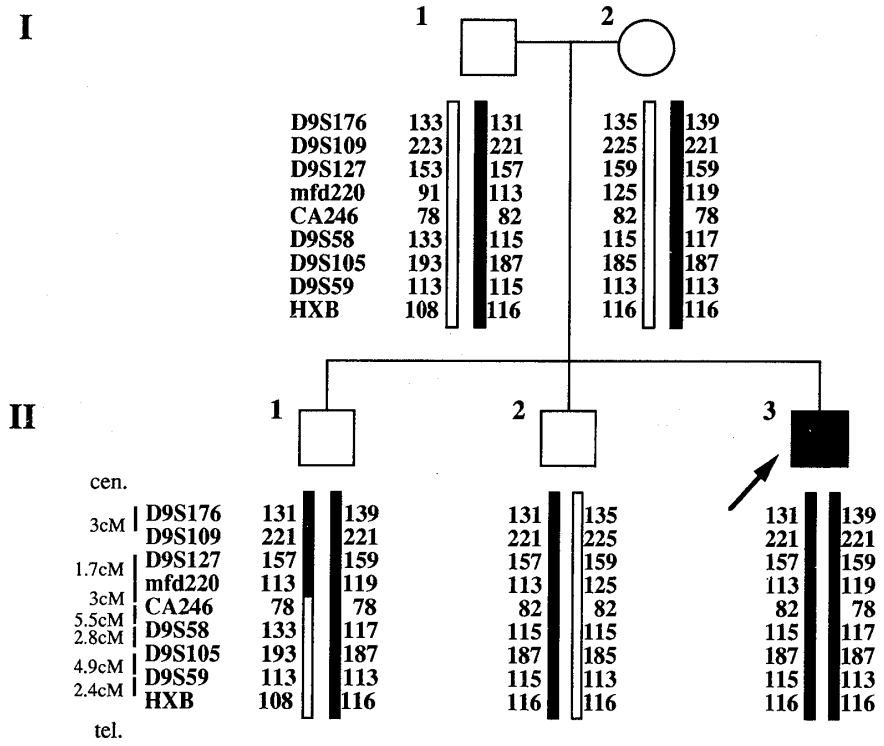

Fig. 6 Genotypes of the present pedigrees

Genotypes are indicated for nine polymorphic microsatelite loci. The FCMD gene is presumed to lie within a region between D9S 127 and CA246. mfd220 is the closest marker with no recombinants. The values shown as haplotypes are the sizes of PCR products obtained with each marker. The haplotype carrying the FCMD gene is shaded. The elder brother (II-1) had inherited a shaded allele from the mother. The paternal allele, which had a crossover, had markers from the centromere side of mfd220 and is also a shaded allele. In the paternal allele, a crossover was identified between loci mfd220 and CA246. The centromere side of mfd220 showed a shaded allele. The other elder brother (II-2) had inherited a shaded allele from the father and a non-shaded allele from the mother. The father (ethnic Japanese, from Aichi prefecture, born in Taiwan), the mother (born in Tokyo) and both elder brothers (born in Tokyo) were examined clinically and all serum CK values were found to be normal.

months of achieving head control and, shortly thereafter, the former acquired the ability to slide on the buttocks. In the latter case, peak motor function was the ability to rotate while in a sitting position. Facial muscle involvement characteristically progressed with aging. The face gradually became thinner, the cheeks atrophied and the lower jaw took on a sharp appearance. Elevation of CK was mild, as compared to FCMD. Head circumferences were relatively large in all three cases.

Discussion

In the more than 15 years which have passed since we first described the striking combination of "pure" CMD with normal mentality and WM hyperlucency on CT scan[1)~3)], more than 50 cases have been reported in the international literature[4)~26)]. A number of these children have, like our original case, shown normal intellectual development in the setting of progressive muscular dystrophy. The heterogeneity evident in this subset of CMD patients, all of whom show WM hyperlucency on CT as well as clinicopathological evidence of central nervous system (CNS) involvement, has been attracting increasing attention worldwide. Topaloglu et al[15)] postulated that these cases constituted a

Table 2 CMD with diffuse white matter hyperlucency and normal mentality

	This case	Additional cases	
		1	2
Sex	M	F	F
Age at first visit	2 y 5m	3 y 4m	9m
Age at last exam.	22 y 7m	5 y 6m	7 y
Age of onset	<3m	<3m	at birth
Family history	healthy siblings	negative for PMD	1C
Head control	9m	11m	7m
Maintain sitting	10m	1 y 6m	11m
Sliding on buttocks	2 y 6m	never	1 y 11m
Peak motor function	sliding on buttocks	rotate in sitting position	sliding on buttocks
Muscle atrophy	+	+	+
Able to support own weight	±	?	±
Muscle weakness	generalized	generalized	generalized
Facial muscle involvement	+	+	+
Joint contracture			
at birth	pes equinovarus	unknown	unknown
at first exam.	hip, ankle, knee	hip, ankle, knee, IP	hip, ankle, knee, elbow
Pseudohypertrophy	−	−	−
PTR	−	−	+ (9m)
Seizures	+ (f.c.)	−	−
IQ	117	125	(normal)
max. CK level	935 (mU/ml)	43.7 (Unit/ml)	246 (mU/ml)
Brain CT	WM hyperlucency	unknown	unknown

WM : white matter, 1C : consanguineous parental marriage (first cousins), PTR : patellar tendon reflexes, CK : creatine kinase, IQ : intelligence quotient, CT : computerized tomography, IP : interphalangel.

clinical entity distinct from FCMD and tentatively applied the term "occidental type cerebromuscular dystrophy". In light of the apparently global distribution of these cases, we prefer the term "pure" CMD with normal mentality and WM hyperlucency but no cerebral dysgenesis. Furthermore, it has now become clear that half of the CMD cases in European countries, including the Turkish cases, have a merosin deficiency[39)~41)], the gene for which is located at 6q2[42)]. Laminin (merosin), a major component of the extracellular matrix, which is linked to the subsarcolemmal cytoskeleton by a large oligomeric complex of dystrophin-associated glycoproteins, could be involved in this form of CMD. Re-biopsy might reveal a merosin deficiency in our original case, who was found to be highly unlikely to have an abnormal gene at the locus of the FCMD gene, but we could not justify this procedure.

The three patients with non-FCMD described herein (though two were not examined by CT, other features were similar among the three cases) represent a homogeneous clinical syndrome affecting both sexes which, like the cases reported by Bernier et al and others[4)~26)], referred to as "pure" CMD with normal mentality and diffuse WM hyperlucency, is characterized by (1) weakness at birth, (2) a slowly improving course until approximately age 10 years, (3) weakness of all muscle groups, (4) weakness of neck flexors leading to marked neck extension, (5) areflexia, (6) elevated blood CK, (7) normal nerve conduction velocity, (8) dystrophic changes on muscle biopsy, and (9) diffuse but predominantly periventricular WM abnormalities. In addition, there is often (1) a family history of a similar disorder, (2) consan-

guineous parental marriage, (3) contractures, such as pes equinovarus, at birth or shortly thereafter, (4) normal intelligence, (5) weakness of muscles innervated by cranial nerves V, VII, IX, X and XI and (6) a brief short-action potential pattern on electromyography[19]. The abnormal motor development observed in our three cases initially manifested with hypotonia, which was apparent in very early infancy. Thereafter, delayed head control was noticed by the parents. Head control was attained between 7m and 11m, followed within a few months by the ability to maintain a sitting posture and, in two cases, to slide on the buttocks. None of our cases was ever ambulant. The clinical course of their muscular dystrophy was slowly progressive. In contract to our extensive experience with FCMD, these three patients did not develop pseudohypertrophy. Facial involvement was also milder, with the face becoming longer and thinner with age, and the serum CK elevation was milder than in FCMD. The tendency, typical of FCMD, for the lips to appear markedly thickened with an everted lower lip, was minimal in these cases. Many FCMD cases, in most of whom skull asymmetry is apparent on CT images, show a plagiocephalic deformity. Based on cephalic index measurements, brachycephalic deformity is common, while dolichocephaly is present in only 13%. The head circumference is generally small and typical FCMD cases never have a circumference greater than the average value. The majority have circumferences smaller than 1 SD below the mean[3]. The head circumference of the case presented in detail here was 1.8 SD above of the mean.

According to the data of Trevisan et al[18] more than half of their cases belong to this group, while we found only three such cases in our experience with approximately 100 CMD cases since 1967.

Our review of the literature on these cases is summarized in Table 3. This review of CMD cases with WM hyperlucency but no other overt CNS abnormalities, and normal or near normal intelligence points to three subgroups into which these patients can be roughly categorized. Those with CMD, WM hyperlucency and normal or only slightly subnormal mentality are represented by the patients reported by Bernier et al[4)5)], Nogen[6)], Egger et al (cases 2 and 3)[8)], Iwashita et al and Koga et al[23)], Castro-Gago et al[9)], Echenne et al (cases 1～4)[11)], Yoshioka et al[24)], Horikawa et al[25)], Streib and Lucking (case 2)[14)], Tanaka et al[26)], Topaloglu et al (cases 1～11)[17)], Trevisan et al[18)], Cook et al (cases 1～5, 8～11)[19)], Pihko et al (cases 5, 6, 11, 26, 28)[21)], and Topaloglu et al (cases 1～15, 19, 20)[22)].

A second category, comprised of patients reported because of a relationship (ex.: a sibling with normal mentality) with the first group, is characterized by mental retardation and epilepsy. This group includes the patients reported by Gobernado and Gimeno[7)], Echenne et al (cases 6 and 7)[12)], Martinelli et al[13)], Topaloglu et al (cases 16 and 18)[17)] and Trevisan et al (case 9)[18)].

Two of the cases reported by Trevisan et al[18)], case 10 in Table 2 and her younger sister (case 9 above), are of particular interest. The elder sister (case 10), who showed mild ventricular dilatation and moderate WM hyperlucency on CT, was above average in intelligence. In contrast, her younger sister (case 9) was mentally retarded, showed severe ventricular dilatation and marked WM hyperlucency on CT and had a seizure disorder with diffuse EEG abnormalities. The seizure disorder, which had begun at age 3y and subsequently become increasingly refractory to treatment, could not account for the marked developmental delay which was apparent before age 2y. Martinelli et al[13)] reported a Mediterranean boy with similar findings, who showed mild intellectual impairment, a seizure disorder with diffuse electroencephalogram (EEG) abnormalities at age 15y, ophthalmoplegia and CMD. Echenne et al[11)] reported the neuropathological findings of a girl (case 7 in their report) with CMD, who had macrocephaly,

Table 3 Review of literature on congenital muscular dystrophy with diffuse white matter hyperlucency and normal mentality

	No. of reported cases	Age	Sex	Family history	Ethnic origin	Age at attainment			CK	MR/IQ	Seizures EEG	WM hyperlucency by repeated CT (age examined)	Others
						HC	keep sitting	ambulant					
Bernier et al[4)5)] ('79)	1~5	11m~ 9y	2F 3M	3 siblings 2 sporadic	European	never without support (4/5)	1y (1/5)	4y (1/5)	2~ 90×	−/?	+absence (2/5) abnormal (5/5)	only once, no difference among patients of different ages	high arched palate, weak at birth, early feeding difficulty, ptosis, long thin face, dolicocephaly & macrocephaly (4/5), early joint contracture
Nogen[6)] ('80)	1	6y	F	sisters, with a healthy younger brother	European		1y	_ 3.5y c support and braces	1.6~3×	−/VIQ111 PIQ 90	?	no change (19m, 42m)	shunted hydrocephalus (elder sister)
	2	1y7m	F			poor	1y1m	1y6m	13×	−/DQ 116	?	less severe than case 1 (5m)	mild visual motor perceptual problem (both sisters)
Egger et al[8)] ('83)	①	14y	F	siblings	European		10m	2y3m	6×	135(8y) 90(10y)	+ abnormal	no change (8y, 11y, 13y)	intellectual deterioration since 8y, never able to run normally, *Brain biopsy : good preservation of cortical architecture, focal subpial gliosis, myelin sheaths were intact but with obvious astrocytic proliferation*
	2	10y	M				7m	3y	3×	−/?	normal	no change (9y, 10y)	slow runner, headache since 10y
	3	5y	F	2C		13m	1y3m	—	3~4×	−/?	normal	progressive (7m, 28m)	*Brain autopsy : patchy demyelination of the centrum semiovale (myelin sheaths showed moderately severe degeneration with unevenness, ballooning and fragmentation) small foci of MPG in parietoccipital and temporal cortex, cerebellum and entire cortex affected by the MPG malformation. Several heterotopic foci (groups of large neurons) were also present in central WM of cerebellar hemispheres* *Generalized neuronal loss, in layer III of cerebral cortex*
Iwashita et al ('82) Koga et al[23)] ('84)	No. 2	15y	M	2C	Japanese	9m	delayed	—	1~4×	−/92	−/abnormal	only once	pes equinovarus & hip joint contractures, *Brain autopsy : localized pachygyria and MPG in bilateral temporal & occipital lobe bases, focal derangement of cerebellar vermis architecture, diffuse myelin pallor*
Castro Gago et al[9)10)] ('85, '88)	1	4y	M	1C	European (Spanish)	8m	1y6m	−	6×	−/?	normal		macrocephaly, mild ventricular dilatation, mild calf pseudohypertrophy, high arched palate, pectus excavatum, elbow, knee, hip contractures, delayed bone age

Echenne et al[11)12)] ('86, '87)	4/10												
	No. 1	ND	F		European (French)		?	−	1.5×	−	?	−	hip dysplasia
	No. 2		M	2 similar sibling cases				3 y	6×	moderate**	normal		WM hyperlucency (limited) dolichocephaly, hight arched palate, hip dysplasia
	No. 3		M	monozygotic				−		moderate**	normal		
	No. 4		M	twins				−		moderate**	?		
	No. 6	20 y	M	sib				+	1.5×		+/abnormal	(17 y)	mild ventricular dilatation (case 6)
	No. 7	18 y	F				1 y 6m	+	1.5×	moderate (70)	+/abnormal	not done	facial weakness, long thin face, disorders of jaw articulation, high arched palate, and macrocephaly (case 6, 7) *Brain autopsy : spongiosis of hemispheric cerebral WM, predominantly in anterior hemispheres (case 7)*
Yoshioka et al[24)] ('87)	1	9 y	M	—	Japanese	9m	9m	−	normal	−/VIQ100 PIQ 90	−/normal	no change (9 y 5m, 10 y 1m)	extremely floppy since birth c poor sucking, contractures of knee joints, long thin face, high arched palate, pigeon chest, ability to roll over attained at 1 y, lost at 8 y
Martinelli et al[13)] ('87)	1	15 y	M	—	Mediterranean			4.5 y	7×	±/70	?/abnormal		neonatal hypotonia worsened after age 5, ophthalmoplegia
Horikawa et al[25)] ('88)	1	10 y	F	—	Japanese		?	−		−/89	?/abnormal	examined only once at 10 y	
Streib et al[14)] ('89)	No. ①	12 y	F	—	European (French)		+	+	5〜10×	−/VIQ88 PIQ92	+/abnormal		*progressive WM disease* decreased visual acuity
	No. 2	27 y	M	affected younger sister			+	+	5×		+/abnormal	no change (23 y, 26 y)	hypotonia at birth, bilateral talipes "benign" CMD
Tanaka et al[26)] ('90)	1	3 y	M	C	Japanese	10m	1 y	−	17×	−	−/abnormal	progressive (7m, 3 y)	weak fetal movement calf pseudohypertrophy
Topaloglu et al[15)〜17)] ('90, '90, '91)		1 y -	4 F	1C/2C (8/11)	Turkish	7m	+ 12m	−	3〜25× (8/11)	−	?		cortical atrophy (7/11 case 1, 2, 4, 5, 6, 8, 9)
	11	12 y	7M	affected sib (2/11)		(case 3)	(case 3)		normal (2/11)	DQ/IQ 79—93	normal (case 3)		multiple joint contractures
Trevisan et al[18)] ('91)	5/12												neonatal onset
	No. 1	16 y 3m	M	—	European (Italian)	5m	10m	−	?	−	−/normal	(5 y)	ventricular dilatation, arachnoid cyst
	No. 5	9 y 3m	F	—		5m	2 y	4 y	?	105	−/normal		*Brain autopsy (case 8) : polygyria in frontal regions, pachygyria in occipital poles, disorganized cytoarchitectonic, small grey heterotopia in WM, laminar areas of demyelination*
	No. 8	6 y	M	—		6m	1 y 2m	−	?	98	−/normal		
	No. 10	2 y 7m	F	+		3m	10m	2 y	?	102	−/normal	(2 y)	ventricular dilatation Elder sister (case 9) mentally retarded (IQ=42) had epilepsy since 3y.
	No. 11	5 y 4m	M	—		7m	12m	−	?	113	−/normal		ventricular dilatation

Cook et al[19] ('92)	No. 1	9y9m	F	sib	Saudi Arabian	6m	1y2m	2y2m	2,1	−/>90	−	8.5y	weakness at birth
	No. 2	7y6m	M	1C		12m	−	−	⟩	−/>90	FC+/normal	CT; less intense*	7/11 roll over at 2y3m (8m ~3y)
	No. 3	3y3m	M	C		12m	2y6m	−	8.5×	−	−	*(4.2y, 7.1y)	
	No. 4	8y4m	F	sib		12m	12m	4y	⟨	−/>90	−	*(1.2y, 2.4y)	9/11 contractures at birth
	No. 5	6y9m	M	1C		12m	12m	−	8.5×	−/>90	−	6.4y	cousins (case 6, 7, product of 1C parents in the reference)
	No. 8	1y7m	F	+		7m	−	−	28~51×	−	−	0.7y	of case 8 have CMD, diffuse
	No. 9	5y4m	F	1C		12m	−	−		−	−	*(4.5y, 5.7y)	hyperlucency in WM by CT,
	No. 10	2y	F	+		12m	2y	−	2,1	−	−/normal	MRI; progressive	but with MR and suffering
									⟩			(12m, 2y4m)	from seizures
	No. 11	1y1m	F	1C		−	−	−	8.5×	−	−	0.8y	
Pihko et al[21] ('92)	5/30	4y			European (Finnish)					−	−/abnormal	No change (5y, 11y)	neonatal hypotonia contractures
	No. 5	5y								−	−/abnormal		
	No. 6									−	+/abnormal		
	No. 11	13y6m	F	sib						−	+/abnormal		
	No. 26	22y8m	M							−	−/slightly abnormal		
	No. 28	25y2m											
Topaloglu et al[22] ('94)	20	1y9m ⟩ 10y10m	12M 8F	3 sibs	Turkish	19/20	19/20	2/20	1~18×	62 ⟩ 105	8/14 abnormal		2 cases c MR (cases 16, 18)

MR: mental retardation, C: consanguinity (1C; first cousins, 2C; second cousins), HC: head control, MPG: micropolygyria, WM: white matter, moderate**: IQ65—75.

mild intellectual impairment (IQ 70) and epilepsy with generalized spike-waves on EEG. No CT scan data were available in this patient, but her brother (case 6), who suffered from the same disease, showed marked WM hyperlucency and slight ventricular enlargement. These cases illustrate the difficulty faced in attempting to categorize CMD cases with normal or near normal intelligence. The sister died at 18y of age and autopsy disclosed marked bilateral and symmetrical myelin pallor in both cerebral hemispheres, predominantly in the frontal lobes. There was severe WM spongiosis, but no other remarkable changes. Histological examination of the brain of Egger et al's third case, who was mentally normal[8], also indicated that the radiographic abnormalities were due to demyelination of the subcortical WM.

A number of the cases presented in Table 3 were found to have CNS abnormalities despite having a normal IQ. As suggested by the two sisters (cases 9 and 10) reported by Trevisan et al[18] and described above, it may be the severity, rather than the presence or absence, of CNS involvement which determines clinical outcome. On the other hand, there are cases, such as our original case in whom genetic analysis essentially ruled out FCMD, who have a clinical entity which is distinctly different from that of CMD associated with cerebral dysgenesis.

There appears to be yet a third category in which the onset of EEG abnormalities or seizures heralds a deterioration in intellectual function. The older (case 1) of the two siblings reported by Egger et al[8], whose IQ deteriorated from 135 at age 8y to 90 at age 10y following the development of an intractable seizure disorder, is a particularly striking example of this course. The girl (case 1) reported by Streib et al[14] showed a slight deterioration in school performance following the development of a seizure disorder which was well controlled with anti-epileptic medications. The authors described this case as having a progressive WM disorder. In these two cases, the WM hyperlucency was associated with clinically apparent

progressive central nervous system impairment and thus might be considered to represent a different disease entity although the younger brother (case 2) of Egger's case 1 did not show any deterioration at age 10. This is an issue which awaits clarification.

Is the WM hyperlucency progressive or static? Our original case, in whom a CT was obtained at age 4y, and again at 20y, showed no evidence of changes in the WM over the intervening 16 years. Diffuse WM hyperlucency was seen on CT scans obtained at an early age, at 5m in one case reported by Nogen[6] and at 7m in one of the cases described by Egger et al[8], and another by Tanaka et al[26], none of whom had any signs or symptoms of CNS disease. All cases (Egger et al's case 3[8], Tanaka et al[26] & Cook et al[19]) in the literature characterized by progression of WM hyperlucency underwent more than one CT examination before age 3y and showed no clinical CNS deterioration. It is possible that an abnormality in the process of myelination is related to progression of WM changes.

What is the relationship between these cases and the well-described forms of CMD associated with cerebral dysgenesis such as FCMD, Santavuori diseases (muscal eye brain disease : MEB), and Walker Warburg syndrome (WWS)? In case 3 reported by Egger et al[8], the case described by Koga et al[23] and case 8 reported by Trevisan et al[18], who were neither mentally retraded nor showed any clinical symptoms and signs suggesting cortical dysplasia, cerebral and cerebellar dysgenesis, specifically micropolygyria or pachygyria, was identified at autopsy. The relationship between these cases and FCMD should be resolved in the future. At present, most "pure" CMD cases with normal mentality and WM hyperlucency are assumed to have a merosin deficiency, based on recent progress in this area of research. A merosin deficiency was not, however, confirmed in these specific cases in which cerebral dysgenesis was present at autopsy despite their normal mentality.

If the underlying abnormality is a merosin deficiency, we must consider the possibility that merosin deficiency might result not only in abnormalities of the myelin sheath but also influence neuronal migration, resulting in a phenotype similar to that of FCMD. FCMD, MEB, and WWS have been speculated to represent different mutations at the same locus although this issue still engenders considerable debate. It is tempting to conclude that CMD cases with normal intelligence represent a clinical entity which is distinct from these forms.

Despite the consistent finding of WM hyperlucency in the patients reviewed herein, clinical heterogeneity is apparent in both intellectual and motor development.

The following points remain to be resolved.

1. Whether those cases with normal or near normal mentality and WM hyperlucency on CT belong to the same disease entity as cases that are mentally retarded and have epilepsy or those who manifest mental deterioration following the onset of EEG abnormalities.

2. Is cerebral dysgenesis, specifically polymicrogyria or pachygyria, a characteristic pathological feature of CMD cases with normal or near normal intelligence? If so, what is the relationship between FCMD and this disease entity?

The relationships among the clinical entities described herein, as well as their relationship with FCMD, MEB and WWS, await clarification.

In 1991, van Engelen et al[43] reported three intellectually-normal siblings with adult-onset muscular dystrophy associated with leukoencephalopathy. In the most severely affected case, a 29y old wheelchair-bound woman, the disorder had manifested at age 18y and progressed slowly thereafter. Her two younger brothers were less severely affected but did show leukoencephalopathy, though of a milder degree, on CT. Repeated CT scanning revealed the leukoencephalopathy to be nonprogressive. The authors concluded that these cases represented a newly-recognized form of autosomal reces-

sively inherited adult-onset CMD. The unusually late onset in these cases provides further evidence of the heterogeneity of CMD associated with WM abnormalities. There are also other reported cases with the combination of WM hyperlucency on CT and muscular dystrophy which seem to belong to yet another disease entity with adult onset, autosomal dominant inheritance and features of inclusion body myositis[44)45)]. We hope that the accumulation of additional clinical data, particularly reports of similar cases, and advances in molecular genetic analysis will shed further light on the significance of WM hyperlucency on CT and the relationships among the various forms of muscular dystrophy discussed in this review.

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知能正常で頭部CT上白質の瀰漫性低吸収域を示す先天性筋ジストロフィーの日本人小児例：16年間経過を追った症例について

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先天性筋ジストロフィー(CMD)という語は，生下時または生後数カ月以内に筋力低下を示し，筋生検ではジストロフィー変化を示す乳児に対し広く用いられてきた．本邦では知能障害を伴う福山型CMDが知られ症例も多い．欧米例は，一般に知能障害は伴わず，筋症状だけを示すと考えられてきた．Nogenが知能は正常であるがCT上白質の瀰漫性の低吸収域を呈するCMD例を報告し，続いて同様の症例が報告され，知能障害は伴わないが中枢神経系に異常のあるCMDの存在が注目を浴びるようになった．1994年にこれらと臨床像が一致する例でメロシンの欠損が認められ，遺伝子座は6q2に存在することが判明した．我々は，生下時より著明な筋力低下を呈し，知能正常，瀰漫性白質低吸収域を呈するCMD例を経験し，1981年CMDII型として報告した．さらに，知能正常，生後まもなく筋力低下を示し，筋生検ではジストロフィー変化を呈する同様な例を3例経験した．いずれも生後3カ月以前に発症し，定頸が7カ月以降と遅れていた．しかしながら，1例を除き坐位保持は1歳未満で獲得しており，いざり這いも可能となった．仮性肥大を認めず，顔筋罹患は軽度に止まり，年長時には顔が細長く見える．1例は，22歳まで経過観察したが，4歳時および19歳時の頭部CTではいずれも瀰漫性白質低吸収域を認め，両所見に差は認めなかった．最高運動機能はいざり這いで，2歳6カ月より11歳まで可能であった．同様の本邦報告例は散見されるが，16年間という長期経過を観察可能であった例は他になく，本邦および欧米例の文献展望を加え，本症の位置付け，分類上の今後の問題点などを検討報告した．