

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/21528>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

## White matter abnormalities in congenital muscular dystrophy <sup>☆</sup>

Q.H. Leyten <sup>a</sup>, F.J.M. Gabreëls <sup>a,\*</sup>, W.O. Renier <sup>a</sup>, B.G.M. van Engelen <sup>a</sup>, H.J. ter Laak <sup>a</sup>,  
R.C.A. Sengers <sup>b</sup>, H.O.M. Thijssen <sup>c</sup>

<sup>a</sup> Institute of Neurology, Department of Child Neurology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>b</sup> Institute of Pediatrics, University Hospital Nijmegen, Nijmegen, The Netherlands

<sup>c</sup> Institute of Diagnostic Radiology, University Hospital Nijmegen, Nijmegen, The Netherlands

Received 30 December 1993; revised 20 July 1994; accepted 7 November 1994

### Abstract

Central nervous system (CNS) characteristics were examined in seventeen patients with autosomal recessive classic or “pure” congenital muscular dystrophy (CMD). In three patients, neuroradiological examination (CT/MRI) indicated hypodense white matter areas. Two out of these three patients had epilepsy (seizures and epileptic discharges on their EEG). Only two of the remaining patients had epileptic EEG discharges, but without clinical seizures. By comparing our results to data in the literature, we could conclude that the classic or “pure” form of CMD can be subdivided into two subtypes, i.e. those with and those without white matter hypodensities. A mild form of epilepsy or an epileptic predisposition on EEG can be part of the subtype with white matter hypodensities.

**Keywords:** Congenital muscular dystrophy; Type 1 congenital muscular dystrophy; Cerebral white matter hypodensity; (Sub)normal intelligence; Epilepsy

### 1. Introduction

Congenital muscular dystrophy (CMD) has been used to describe a group of neuromuscular disorders characterized by autosomal recessive inheritance, onset at birth or during the first year of life, hypotonia and generalized muscular weakness, multiple joint contractures evident in the first year of life, non-progressive or slowly progressive clinical course, (sub)normal mental development, and muscle biopsies which show striking pathological changes similar to muscular dystrophy and a normal distribution of dystrophin (Fukuyama et al., 1960, 1981; Gubbay et al., 1966; Vassella et al., 1970; Donner et al., 1975; Lazaro et al., 1979; Serratrice et al., 1980; McMenamin et al., 1982; Banker, 1986; Dubowitz, 1994). CMD has been classified into three separate entities (Dubowitz, 1994): classic or “pure”

CMD with (sub)normal intelligence, Fukuyama type of CMD (F-CMD) with cerebral abnormalities and severe mental retardation (Fukuyama et al., 1960, 1981), and “muscle-eye-brain disease” (MEB-D) (Raitta et al., 1978; Santavuori et al., 1989; Leyten et al., 1991, 1992) or the “cerebro-ocular dysplasia-muscular dystrophy syndrome” (COD-MD) (Towfighi et al., 1984; Heggie et al., 1987; Federico et al., 1988) with severe mental retardation and ocular malformations. The Walker-Warburg syndrome (WWS) is an autosomal recessive disorder characterized by type II lissencephaly, cerebellar malformation, characteristic eye malformations and congenital muscular dystrophy (McKusick, 1988). At present, there is still no consensus about whether MEB-D and WWS are separate entities (Dubowitz, 1994). Some authors consider that MEB-D and WWS only differ in severity rather than in any fundamental feature (Dobyns et al., 1985; Leyten et al., 1989).

Recently, there have been 14 reports on 64 patients with a “pure” CMD and (sub)normal intelligence, whose CT/MRI scans indicated marked hypodensity of the white matter (Bernier et al., 1979; Nogen, 1980;

<sup>☆</sup> This investigation is part of the research programme on “Disorders of the Neuromuscular System” of the University of Nijmegen.

\* Corresponding author. Tel.: (+31-80) 614894; Fax: (+31-80) 540576.

Egger et al., 1983; Echenne et al., 1986; Martinelli et al., 1987; Yoshioka et al., 1987; Castro-Gago and Peña-Gutián, 1988; Streib and Lucking, 1989; Tanaka et al., 1990; Cook et al., 1992; Kaciński et al., 1992; Pihko et al., 1992; Donner [see Dubowitz, 1994]; Topaloğlu et al., 1994). Topaloğlu et al. (1994) suggested that this type should be considered as an intermediate form between the “pure” form of CMD and the Fukuyama type of CMD, referred to by them as “occidental type cerebromuscular dystrophy”. At present, cases with a (sub)normal intelligence quotient (IQ) who show white matter hypodensity on CT or MRI examination are included into the “pure” form of CMD (Dubowitz, 1994).

We analyzed the CT/MRI of our 17 patients with “pure” CMD and found 3 cases with white matter hypodensities. The clinical, electrophysiological and neuroradiological data on these patients were compared to those reported in the literature.

## 2. Materials and methods

In a retrospective study on a consecutive series of 2010 patients who underwent muscle biopsy because of muscle weakness, we found 17 patients with CMD. The final diagnosis was based on diagnostic criteria for classic or “pure” CMD (see Table 1) (Dubowitz, 1994). CNS characteristics of these patients were analyzed, including the clinical signs and symptoms, IQ, cerebrospinal fluid (CSF) (9 patients), especially myelin basic protein (MBP), EEG, and neuroradiological findings (CT/MRI). DNA analysis including examination of the Xp 21 dystrophy gen was performed on all of the boys with a serum creatine kinase (CK) level of above 150 U/l (normal, < 100 U/l), on some of the boys with a normal CK level and on two of the girls.

### 2.1. Report of 3 CMD cases with white matter hypodensities

#### Case 15

This 21-year-old man was the only child of healthy non-consanguineous parents. Family history did not mention neuromuscular disorders. Pregnancy was uneventful with normal intrauterine movements. Birth weight was 2870 g. At birth, generalized weakness and hypotonia, facies myopathica and contractures of the hips were found. Respiration was poor during the neonatal period. Motor development was delayed; the patient sat without support at 36 months and pulled himself upright at 40 months. He did not learn to stand and walk without support. Intellectual development was normal.

On admission at 3 years of age, muscle weakness and hypotonia were severe and diffuse, but muscle wasting was not obvious. His face was without expression. Flexion contractures of the elbow, knee, hip and ankle joints were present. Right concave scoliosis was found. The only abnormal neurological signs comprised absent tendon reflexes, while the plantar responses were flexor. There were no dysmorphic features and the head circumference was on the 50th percentile. His mental development was considered to be above average until the age of 3 years.

On examination at the age of 13 years, there was no evidence of progression of the muscle weakness. The Wechsler Intelligence Scale for Children-Revised (WISC-R) revealed a full scale IQ score of 115.

At the age of 20 years, muscle weakness was static. He did not show deterioration in intelligence and behaviour. At this age, he had suffered two generalized tonic-clonic grand mal epileptic seizure. Over the last four years he developed progressive thoracic scoliosis.

Biochemical investigations of serum and urine gave

Table 1  
Diagnostic criteria for classic or “pure” CMD.

Inclusion criteria	Exclusion criteria
<p>Clinical features:</p> <ul style="list-style-type: none"> <li>– onset at birth or during the first year of life,</li> <li>– hypotonia and generalized muscular weakness,</li> <li>– multiple joint contractures evident in the first year of life,</li> <li>– clinical course non-progressive or slowly progressive,</li> <li>– normal or subnormal mental development.</li> </ul> <p>Muscle biopsy:</p> <ul style="list-style-type: none"> <li>– dystrophic pattern,</li> <li>– marked increase in interstitial connective tissue with or without increase in interstitial adipose tissue,</li> <li>– no marked fibre necrosis and regenerative activity,</li> <li>– sometimes more pronounced dystrophic pattern, with evident necrosis and regeneration; dystrophin (both immunocytochemical and Western blot) must be present and normal.</li> </ul>	<p>Clinical features:</p> <ul style="list-style-type: none"> <li>– onset during childhood,</li> <li>– clinical course rapidly progressive,</li> <li>– muscular hypertrophy,</li> <li>– ptosis and/or ophthalmoplegia,</li> <li>– severe impairment of intellectual development (IQ &lt; 50),</li> <li>– ocular abnormalities.</li> </ul> <p>Laboratory findings:</p> <ul style="list-style-type: none"> <li>– EMG with “neuropathic” pattern,</li> <li>– muscle biopsy normal, with neuropathic abnormalities or with structural abnormalities specific of other myopathies,</li> <li>– dystrophin absent or abnormal,</li> <li>– major CT or MRI abnormalities of CNS different from white matter hypodensity (major malformations, developmental and/or migration defects),</li> <li>– ocular abnormalities showed by ophthalmological examination.</li> </ul>

normal values except for a serum CK of 400 U/l (normal, <100 U/l). Full blood count, electrolytes, lactate and pyruvate levels in serum and CSF, blood and urine amino acids, copper, long chain fatty acids, white cell lysosomal enzymes and organic acids were normal. Microbiological examination excluded infections such as toxoplasma, cytomegalovirus, herpes or rubella virus. Chromosome analysis revealed a normal 46,XY karyotype. Rearrangements of the dystrophy gen at Xp21 were not found.

Electromyography (EMG) revealed an increased number of brief polyphasic potentials with a small amplitude. Motor nerve conduction velocities were normal. EEG showed rhythmic activity which was poor for his age and multifocal discharges. VEP and SSEP were normal.

A biopsy from the quadriceps muscle at the age of 3 years showed a wide variation in fibre diameters; many of the fibres were larger than normal. Degenerative changes were present with central nuclei and fibre splitting. There was an increase in the interstitial connective tissue and some fat replacement.

Cerebral CT at the age of 13 years showed marked hypodensity of the white matter of both hemispheres, which could also be seen on MRI. There has been no progression in white matter hypodensities on CT/MRI during the past 5 years.

#### Case 16

A boy, the third child of healthy consanguineous parents (second cousins), was born after an uneventful pregnancy and normal intrauterine movements. Family history did not mention any neuromuscular disorders. Birth weight was 3925 g. Postpartum period was not complicated by asphyxia. At birth, generalized weakness and hypotonia, facies myopathica and contractures were found. Since the age of 2 years, he has been receiving (successful) treatment with antiepileptic drugs for partial complex epileptic seizures, sometimes with secondary generalization.

On examination at the age of 6 years, his head circumference was 55 cm (> P90) and strabismus divergens was noted, without any structural ocular malformations. Generalized hypotonia and muscle weakness, which affected the proximal and distal muscles equally, were present with "facies myopathica". Deep tendon reflexes could not be elicited. Examination of the feet revealed "pedes equinovarus adducti" with toe-walking. Further development was characterized by motor retardation and contractures of the achilles tendons which necessitated tendon lengthening procedures. At the age of 7 years, he became wheelchair-dependent. Over the past 8 years he has developed progressive thoracolumbar scoliosis which required spondylodesis. At present he is 22 years old and wheelchair-depend-

dent. He did not show any deterioration in intelligence and behaviour.

Biochemical investigations of serum and urine gave normal values (CK, 67 U/l). Full blood count, electrolytes, lactate and pyruvate levels in serum and CSF, blood and urine amino acids, copper, long chain fatty acids, white cell lysosomal enzymes and organic acids were normal. Microbiological examination excluded infections such as toxoplasma, cytomegalovirus, herpes or rubella virus. Chromosome analysis revealed a normal 46,XY karyotype. Rearrangements of the dystrophy gen at Xp21 were not found.

EMG revealed an increased number of brief polyphasic potentials with a small amplitude. Motor nerve conduction velocities were normal. EEG showed diffuse slowing of the background and paroxysmal epileptic discharges.

A biopsy from the quadriceps muscle at the age of six years revealed dystrophic changes, such as increased variability of muscle fibre size, severe increase of fat cells, basophilic fibres and fibres with internal nuclei and an increased amount of interstitial connective tissue.



Fig. 1. Cerebral CT scan of case 16 showing diffuse hypodensity of the white matter.

Cerebral CT at the age of 12 years showed diffuse hypodensity of the white matter (Fig. 1). MRI of the brain was not performed. No progression of the white matter hypodensities has been seen on CT during the past 3 years.

### Case 17

A girl, the third child of healthy non-consanguineous parents, was born after an uneventful pregnancy with normal intrauterine movements. Family history did not mention any neuromuscular disorders. Birth weight was 3360 grams and the Apgar scores were 9 and 10. Postpartum period was not complicated by asphyxia. At birth, generalized weakness and hypotonia, facies myopathica and slight dysplasia of the left hip were found. Deep tendon reflexes were absent. Head circumference was normal for her age. Ophthalmological examination did not reveal any structural malformations. At the age of 3 months, torticollis was noted, which necessitated operative correction at the age of 7 months. By the age of 18 months she was able to crawl, but could not stand. Generalized areflexia, hypotonia and muscle weakness were obvious, especially in the proximal musculature. Contractures did not occur. Mental development was normal. The following examinations were performed at this age of 18 months.

Biochemical investigations of serum and urine gave normal values, except for increased CK (1178 U/l, normal < 90). Full blood count, electrolytes, lactate and pyruvate levels in serum and CSF, blood and urine amino acids, copper, long chain fatty acids, white cell lysosomal enzymes and organic acids were normal. Microbiological examination excluded infections such as toxoplasma, cytomegalovirus, herpes or rubella virus. Chromosome analysis revealed a normal 46,XX karyotype. Rearrangements of the dystrophy gen at Xp21 were not found.

EMG revealed an increased number of brief polyphasic potentials with a small amplitude. Nerve conduction velocity was normal. EEG, VEP and BAEP were normal.

A biopsy from the quadriceps muscle at the age of 18 months revealed dystrophic changes, such as rounded fibres, a wide variation in the fibre diameter and an increased amount of interstitial connective tissue (Fig. 2A). There was no marked evidence of fibre necrosis and regenerative activity. Immunohistochemistry with dystrophin antibodies showed a normal expression pattern (Fig. 2B).

Cerebral CT at the age of 18 months showed hypodensities in the white matter. At this age, MRI revealed hypodensities in the periventricular areas of both occipital horns (T1, sagittal) and hyperintensity of the white matter (T2). No progression in white matter hypodensities has been seen on CT/MRI during the past 3 years.

Clinical course was characterized by motor retardation, but with normal mental development.

### 3. Analysis of data on 17 CMD patients (Table 2)

#### Neuroradiological findings

Thirteen patients did not show abnormalities on their CT or MRI of the brain. In the 3 patients (cases 15, 16 and 17) with white matter hypodensity on cerebral CT, the hypodensity was diffuse and could be confirmed in 2 of the 3 cases by MRI; in one patient, MRI was not available (case 16). The first neuroimaging occurred at the age of 1.5, 13 and 16 years, respectively. Follow-up was performed 3, 5 and 3 years later, respectively. There was no change or progression.

#### Clinical features

There were no clinical differences between CMD with and without white matter abnormalities.

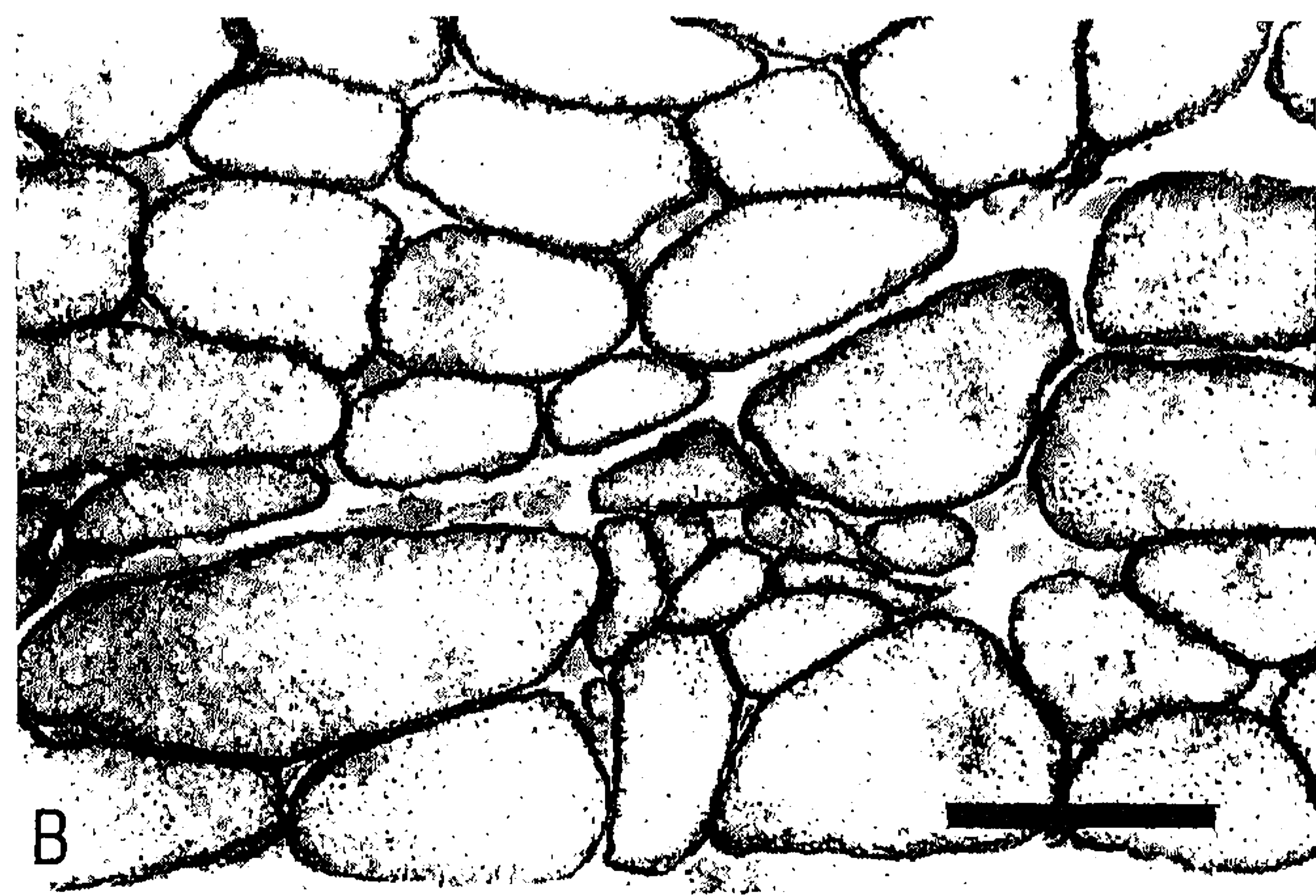
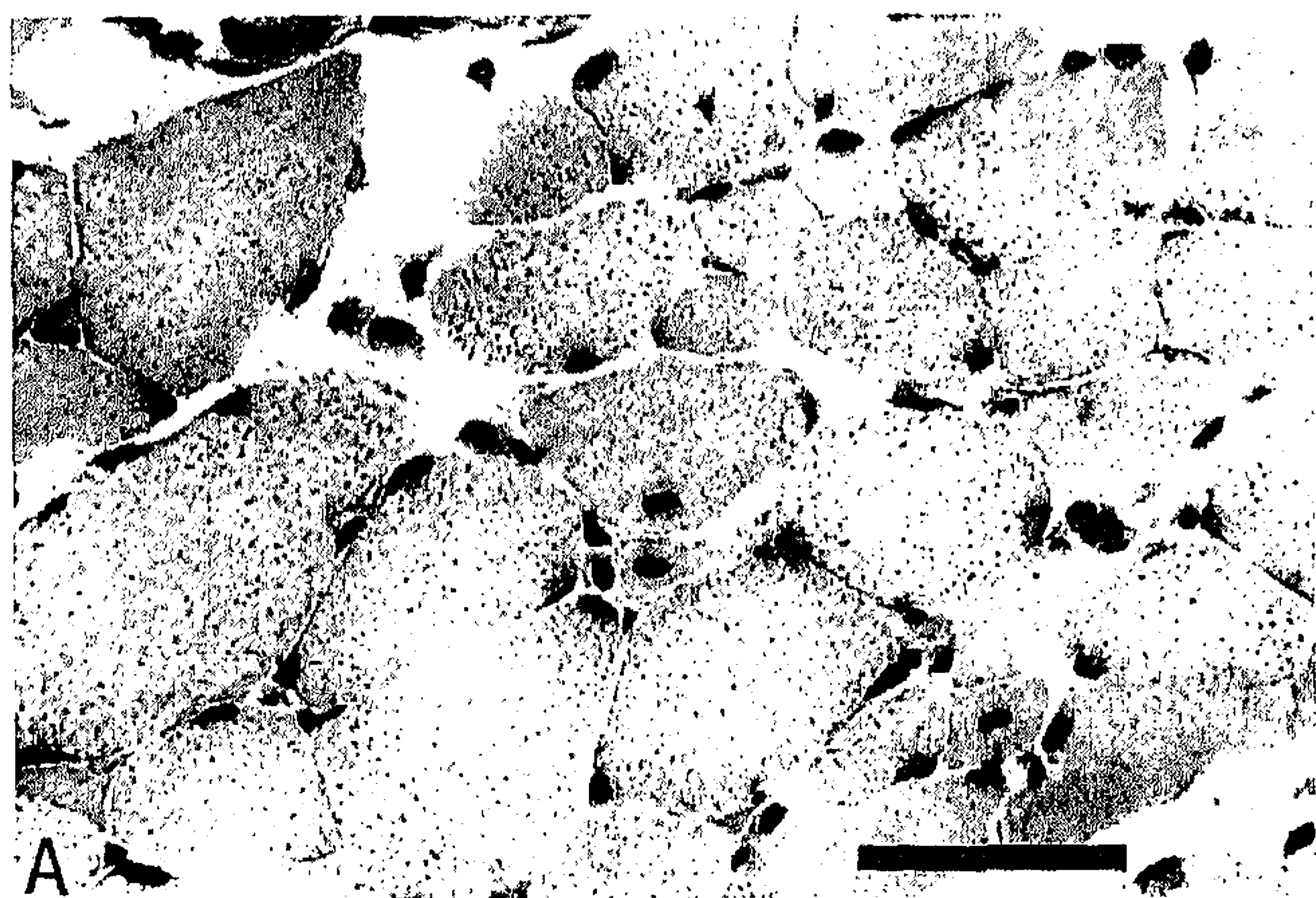


Fig. 2. Biopsy of quadriceps muscle stained with HE (A) and dystrophin antibody (B). Note the wide variation of muscle fibre diameters and the even distribution of dystrophin. Bar = 50  $\mu$ m.

Table 2  
Signs and symptoms, laboratory, genetical, radiological, and neurophysiological characteristics of 17 patients with “pure” congenital muscular dystrophy, 3 of whom had white matter hypodensities

Case No.	“Pure” CMD																
	Without white matter hypodensity														With white matter hypodensity		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age at muscle biopsy (yr)	0	0	1	1	1	2	3	3	3	3	4	5	6	14	3	6	1
Sex	F	M	F	F	F	M	M	M	M	M	M	M	M	M	M	M	F
Consanguinity	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–
Congenital hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Joint contractures	+	–	–	+	+	–	–	+	–	–	–	–	–	+	+	+	–
Rapidly progressive course (motor retardation)	+	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–
CK activity (normal < 100 U/l)	288	N	N	N	N	N	N	143	N	N	134	153	392	N	400	N	1178
DNA analysis	np	np	np	N	np	np	N	np	np	N	np	N	N	np	N	N	N
Dystrophic muscular biopsy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CNS involvement																	
– CSF abnormalities	np	np	N	np	N	N	N	np	N	N	np	np	N	np	np	N	N
– EEG abnormalities	–	–	–	np	–	–	–	+	+	–	–	–	–	–	+	+	–
– convulsions / epilepsy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–
– hypomyelination (CT/MRI)	np	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+
– intelligence *	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

N = normal; np = not performed; – = absent; + = present. \* Normal intelligence = IQ > 70.

Table 3  
Review of previously reported cases (64) and our cases (3) of congenital muscular dystrophy with (sub)normal intelligence and low density areas in the white matter.

	(First) author (year of publication)															Our cases	Total
	Bernier (1979)	Nogen (1980)	Egger (1983)	Echenne (1986)	Martinelli (1987)	Yoshioka (1987)	Castro-Gago (1988)	Streib (1989)	Tanaka (1990)	Kaciński (1992)	Cook (1992)	Pihko (1992)	Donner *	Topaloglu (1994)			
Number of cases	5	2	3	6	1	1	1	2	1	1	11	5	5	20	3	67	
Male : female ratio	3 : 2	0 : 2	1 : 2	4 : 2	1 : 0	1 : 0	1 : 0	1 : 1	1 : 0	0 : 1	4 : 7	3 : 2	nm	12 : 8	2 : 1	34 : 28	
Weakness																	
– nonprogressive	5/5	2/2	2/3	4/6	0/1	1/1	1/1	2/2	1/1	1/1	2/11	5/5	nm	3/20	2/3	31/62	
– progressive	0/5	0/2	1/3	2/6	1/1	0/1	0/1	0/2	0/1	0/1	9/11	0/5	nm	17/20	1/3	31/62	
Epilepsy	1/5	0/2	1/3	2/6	1/1	0/1	0/1	2/2	0/1	0/1	0/11	2/5	3/5	1/20	2/3	15/67	
IQ > 70	5/5	0/2	3/3	1/6	1/1	1/1	1/1	2/2	1/1	1/1	9/11	5/5	5/5	11/13	3/3	49/60	
50–70	0/5	2/2	0/3	5/6	0/1	0/1	0/1	0/2	0/1	0/1	2/11	0/5	0/5	2/13	0/3	11/60	
Other clinical signs																	
– dysmorphic features **	0/5	0/2	0/3	0/6	0/1	1/1	0/1	0/2	0/1	0/1	0/11	0/5	nm	8/20?	0/3	9/62	
– pyramidal syndrome	0/5	0/2	0/3	0/6	0/1	0/1	0/1	1/2	0/1	0/1	0/11	0/5	nm	0/20	0/3	1/62	
Epileptic EEG	1/5	0/2	1/3	2/4	1/1	0/1	0/1	2/2	0/1	0/1	1/4	5/5	nm	8/20?	2/3	23/53	

F = female; M = male; nm = not mentioned. \* See Dubowitz 1994. \*\* Dysmorphic features, such as (long and) thin face, high arched palate, abnormalities of jaw articulation, and pigeon chest.

### EEG and epilepsy

In cases 8 and 9, generalized spike-wave paroxysms occurred during sleep. In case 8, there were also some spikes of short duration in the central regions, while in case 9, paroxysmal sharp theta waves were found, but these electrical phenomena were not associated with seizures.

Two patients with white matter hypodensities (cases 16 and 17) had poor rhythmic background activity for their age. In cases 16 and 17, the following were noted: multifocal discharges, diffuse slowing of the background activity and paroxysmal epileptic discharges, such as bilateral irregular sharp theta waves which were sometimes mingled with spikes. Both patients had clinical seizures. Case 16 had suffered from two generalized tonic-clonic epileptic seizure at the age of 20 years, while case 17 had suffered partial complex seizures sometimes with secondary generalization from the age of 2 years onwards. Seizures could be treated successfully using conventional antiepileptic drugs.

### Laboratory findings

In 16 out of our 17 patients, serum CK activity appeared to be normal or slightly increased. One case (case 17) with cerebral white matter hypodensity had markedly increased CK activity.

All the CSF parameters, including cell count, protein content, protein electrophoresis, immuno-electrophoresis, myelin basic protein, lactate and pyruvate levels, were within normal ranges.

### Genetics

The male/female ratio was 12:5. In 2 patients, consanguinity could be proved (case 5, 8th–9th generation; case 17, second cousins).

DNA analysis was performed on 6 boys and 2 girls. Rearrangements of the dystrophy gen at Xp21 were not found.

## 4. Discussion

Congenital muscular dystrophy may be associated with more or less marked disorders of cerebral development. There are three subtypes (Dubowitz, 1994): classic or “pure” CMD, F-CMD and MEB-D. Topaloğlu et al. (1994) believe that CMD with only white matter hypodensities on CT or MRI examination should be considered as an intermediate form. However, according to the opinion of most of the participants in a workshop on this topic (Dubowitz, 1994), cases with a (sub)normal IQ who show white matter hypodensities on CT or MRI, without major malformations, developmental and/or migration defects of CNS, should be included in the classic or “pure” form of CMD (see Table 1).

Table 2 shows a summary of the clinical data published in the literature on patients with CMD, (sub)normal intelligence, and low density areas in the white matter. All 17 patients with CMD in our series showed normal intellectual development. Three had marked, diffuse hypodensity of the white matter on CT and/or MRI examination. There were no dysmorphic features and no pyramidal signs. Some reports mentioned dysmorphic features, such as a long and thin face, abnormalities of jaw articulation and a high arched palate (Yoshioka et al., 1987; Topaloğlu et al., 1994). Although the authors of these reports suggested that these clinical aspects are specific, we believe that the facial dysmorphic features and high arched palate are not specific for this group, but they are frequently seen in myopathic children (Leyten et al., 1990). Topaloğlu et al. (1994) reported clinical findings in 18 cases with “pure” CMD and 20 cases with (sub)normal IQ which show white matter hypodensity. The last group may tend to run a more severe course in the presence of significantly higher CK levels. This is in agreement with our findings.

EEG abnormalities are not uncommon in “pure” CMD. Spikes and slow waves, periodic complexes and focal spikes can be detected in the routine EEG recordings (Pihko et al., 1992; Topaloğlu et al., 1994). In literature 21 of 50 studies cases with hypodensity of the white matter had abnormal recordings (see Table 3). Two of our three patients (cases 15 and 16) had seizures and epileptic discharges on their EEG. In contrast, only 2 of the 14 remaining CMD cases (cases 8 and 9) had epileptic EEG discharges without any seizures. However, only CT but no MRI examination of the brain had been performed on these patients, so we cannot exclude minor CNS deficit which can only be visualized using MRI.

The occurrence of epilepsy was mentioned in 13 out of 64 patients in the literature (Table 3). Based on the data presented in Table 3, it can be concluded that there is a significantly higher epilepsy ratio (1 : 4.5) in CMD patients with (sub)normal intelligence and associated white matter hypodensities than in the normal population (1 : 150). This phenomenon cannot be explained by other neurological pathology. Therefore we believe that a mild form of epilepsy can be part of CMD with white matter hypodensities.

The nature and significance of the white matter changes remain obscure. Informative neuropathological data are scarce. There is only one report (Egger et al., 1983) which described two patients. One patient showed moderate focal subpial gliosis and good preservation of the cortical architecture in a brain biopsy from the right frontal lobe. The myelin sheaths were intact in the core of the convolution. In the white matter, there was obvious astrocytic proliferation. This patient had a WISC-IQ of 135 at the age of 8 years,

but this had fallen to 90 at the age of 10 years. In the other patient in the report, microscopical examination showed patchy demyelination of the white matter of the centrum semiovale. The authors suggest that these neuropathological findings in themselves were not diagnostic, but the low density in the central areas of the brain on the CT scans may indicate a demyelinating process. One other case had spongy appearance of white matter on necropsy (Echenne et al., 1986). Malik et al. (1990) described a case with significant decrease in staining of myelin as compared with age-matched, normal control brains. Before the introduction of CT/MRI, other authors also found demyelination of the brain in congenital muscular dystrophy (Fowler and Manson, 1973). However, the lack of progression of white matter hypodensities on successive CT/MRI scans (Egger et al., 1983; Streib and Lucking, 1989; Cook et al., 1992; our study), the absence of progressive neurological signs and symptoms, and the normal MBP findings in CSF in our patients, are all arguments in favour of a non-progressive cerebral white matter disorder. However long-term follow-up studies and neuropathological studies will be necessary to have more insight in this topic.

The histological findings in the muscle biopsy specimens from CMD patients with (sub)normal intelligence and low density areas in the white matter reported in the literature and the findings in our series (Table 3) did not differ essentially from those described in "pure" CMD, F-CMD and MEB-D (Leyten et al., 1993). In their series, Topaloğlu et al. (1994) found necrosis in 4 patients with white matter hypodensity and not in "pure" CMD. In our series, only fat cell infiltration was found to be increased with increasing age in "pure" CMD (Leyten et al., 1993). Therefore, muscle biopsies cannot discriminate between the subtypes of CMD.

In conclusion, the data published in the literature (Table 3) and our findings support the hypothesis that the "pure" form of CMD with (sub)normal mental development can be subdivided into two subtypes, i.e. those with and those without white matter hypodensities. However, considerable overlap is evident in clinical and pathological presentations. The subtype with white matter hypodensities tend to be clinically more severe (Topaloğlu et al., 1994) and a mild form of epilepsy can be part of the clinical picture. The features are not sufficient to consider this subtype of CMD as an separate entity between the "pure" form of CMD and the Fukuyama type of CMD (Dubowitz, 1994).

Further research should aim to perform more MRI in a prospective longitudinal way, at different ages and on larger groups of children with CMD, and should include neuropathological examination of the hypodense white matter areas. Molecular genetic studies ("genetic mapping") should help to clarify whether the

possible etiologic heterogeneity in the three subtypes of CMD is caused by allelic mutations of the same gene or by mutations in different genes. The responsible gene for the Fukuyama type of CMD has been localized at chromosome 9q31-33 (Toda et al., 1993) and we are probably now reaching the stage with CMD having clearly defined basic syndromes.

### Acknowledgement

We thank Mrs. Patricia L. Hill for linguistic advice.

### References

- Banker, B.Q. (1986) Congenital muscular dystrophy. In: A.G. Engel and B.Q. Banker (Eds.), *Myology*, vol. 2, McGraw-Hill, New York, pp. 1367–1382.
- Bernier, J.-P., M.H. Brooke, T.P. Naidich and J.E. Carroll (1979) Myoencephalopathy: cerebral hypomyelination revealed by CT scan of the head in a muscle disease. *Trans. Am. Neurol. Assoc.*, 104: 244–246.
- Castro-Gago, M. and J. Peña-Gutián (1988) Congenital muscular dystrophy of a non-Fukuyama type with characteristic CT images (letter). *Brain Dev.*, 10: 60.
- Cook, J.D., G.G. Gascon, A. Haider, R. Coates, B. Stigsby, P.T. Ozand and M. Banna (1992) Congenital muscular dystrophy with abnormal radiographic myelin pattern. *J. Child Neurol.*, 7 (Suppl.): 51–63.
- Dobyns, W.B., J.B. Kirkpatrick, H.M. Hittner, R.M. Roberts and F.L. Kretzer (1985) Syndromes with lissencephaly. II. Walker-Warburg and cerebro-oculo-muscular syndromes and a new syndrome with type II lissencephaly. *Am. J. Med. Genet.*, 22: 157–195.
- Donner, M., J. Rapola and H. Somer (1975) Congenital muscular dystrophy: a clinico-pathological and follow-up study of 15 patients. *Neuropädiatrie*, 6: 239–258.
- Dubowitz, V. (1994) Workshop report. 22nd ENMC Sponsored Workshop on Congenital Muscular Dystrophy held in Baarn, The Netherlands, 14–16 May 1993. *Neuromusc. Disord.*, 4: 75–81.
- Echenne, B., M. Arthuis, C. Billard, J. Campos-Castello, Y. Castel, O. Dulac, D. Fontan, A. Gauthier, G. Kulalowski, G. De Meuron, J.R. Moore, M. Nieto-Barrera, M. Pages, D. Parain, L. Pavone and G. Ponsot (1986) Congenital muscular dystrophy and the cerebral CT scan anomalies. *J. Neurol. Sci.*, 75: 7–22.
- Egger, J., B.E. Kendall, M. Efdohazi, B.D. Lake, J. Wilson and E.M. Brett (1983) Involvement of the central nervous system in congenital muscular dystrophy. *Dev. Med. Child Neurol.*, 25: 32–42.
- Federico, A., M.T. Dotti, A. Malandrini, G.C. Guazzi, G. Hayek, H. Simonati, N. Rizzuto and P. Toti (1988) Cerebro-ocular dysplasia and muscular dystrophy: report of two cases. *Neuropediatrics*, 19: 109–112.
- Fowler, M.C. and J.I. Manson (1973) Congenital muscular dystrophy with malformations of the central nervous system. In: B.A. Kaku-las (Ed.), *Clinical Studies in Myology*, ICS 295, Excerpta Medica, Amsterdam, pp. 192–197.
- Fukuyama, Y., M. Kawazura and H. Haruna (1960) A peculiar form of congenital progressive muscular dystrophy: report of fifteen cases. *Pediatr. Univ. Tokyo*, 4: 5–8.
- Fukuyama, Y., M. Osawa and H. Suzuki (1981) Congenital progressive muscular dystrophy of the Fukuyama type: clinical, genetic and pathological considerations. *Brain Dev.*, 3: 1–29.



- Gubbay, S.S., J.N. Walton and G.W. Pearce (1966) Clinical and pathological study of a case of congenital muscular dystrophy. *J. Neurol. Neurosurg. Psychiat.*, 29: 500–508.
- Heggie, P., H.E. Grossniklaus, U. Roessmann, S.M. Chou and R.P. Cruse (1987) Cerebro-ocular dysplasia-muscular dystrophy syndrome: report of two cases. *Arch. Ophthalmol.*, 105: 520–524.
- Kaciński, M., B. Bańdo, S. Krocza and M.M. Malinowska-Matuszewska (1992) A case of congenital muscular dystrophy with changes in the white matter of the brain. *Neurol. Neurochir. Pol.*, 26: 383–387 (in Polish).
- Lazaro, R.P., G.M. Fenichel and A.W. Kilroy (1979) Congenital muscular dystrophy: case reports and reappraisal. *Muscle Nerve*, 2: 349–355.
- Leyten, Q.H., F.J.M. Gabreëls, W.O. Renier, H.J. ter Laak, R.C.A. Sengers and R.A. Mullaart (1989) Congenital muscular dystrophy. *J. Pediatr.*, 115: 214–221.
- Leyten, Q.H., F.J.M. Gabreëls and W.O. Renier (1990) Classification of congenital muscular dystrophy (letter in reply to H. Topaloğlu, Y. Renda, K. Yalaz, K. Gücüyener, M. Çağlar, S. Göğüs and G. Kale). *J. Pediatr.*, 117: 166–167.
- Leyten, Q.H., K. Renkawek, W.O. Renier, F.J.M. Gabreëls, C.M. Mooy, H.J. ter Laak and R.A. Mullaart (1991) Neuropathological findings in muscle-eye-brain disease (MEB-D): neuropathological delineation of MEB-D from congenital muscular dystrophy of the Fukuyama type. *Acta Neuropathol. (Berl.)*, 83: 55–60.
- Leyten, Q.H., F.J.M. Gabreëls, W.O. Renier, K. Renkawek, H.J. ter Laak and R.A. Mullaart (1992) Congenital muscular dystrophy with eye and brain malformations in six Dutch patients. *Neuropediatrics*, 23: 316–320.
- Leyten, Q.H., H.J. ter Laak, F.J.M. Gabreëls, W.O. Renier and R.C.A. Sengers (1993) Congenital muscular dystrophy: a study on the variability of morphological changes and dystrophin distribution in muscle biopsies. *Acta Neuropathol. (Berl.)*, 86: 386–392.
- Malik, S., R.P. Cruse, S.M. Chou and T. Chafel (1990) Non-Fukuyama congenital muscular dystrophy with central nervous system involvement: clinical, radiographic and pathological correlates (abstract). *Ann. Neurol.*, 28: 430.
- Martinelli, P., A.S. Gabellini, G. Ciucci, E. Govoni, S. Vitali and M.R. Gulli (1987) Congenital muscular dystrophy with central nervous system involvement: case report. *Eur. Neurol.*, 26: 17–22.
- McKusick, V.A. (1988) Mendelian Inheritance in Man, 8th edn., Johns Hopkins University Press, Baltimore–London, entry 23667.
- McMenamin, J.B., L.E. Becker and E.G. Murphy (1982) Congenital muscular dystrophy: a clinicopathologic report of 24 cases. *J. Pediatr.*, 100: 692–697.
- Nogen, A.G. (1980) Congenital muscle disease and abnormal findings on computerized tomography. *Dev. Med. Child Neurol.*, 22: 658–663.
- Pihko, H., T. Louhimo, L. Valanne and M. Donner (1992) CNS in congenital muscular dystrophy without mental retardation. *Neuropediatrics*, 23: 116–122.
- Raitta, C., M. Lamminen, P. Santavuori and J. Leisti (1978) Ophthalmological findings in a new syndrome with muscle, eye and brain involvement. *Acta Ophthalmol. (Copenh.)*, 56: 465–472.
- Santavuori, P., H. Somer, K. Sainio, J. Rapola, S. Kruus, T. Nikitin, L. Ketonen and J. Leisti (1989) Muscle-eye-brain disease. *Brain Dev.*, 11: 147–153.
- Serratrice, G., D. Cros, J.-F. Pellissier, J.-L. Gastaut and J. Pouget (1980) Dystrophie musculaire congénitale. *Rev. Neurol. (Paris)*, 136: 445–472.
- Streib, E.W. and C.H. Lucking (1989) Congenital muscular dystrophy with leukoencephalopathy. *Eur. Neurol.*, 29: 211–215.
- Tanaka, J., T. Mimaki, S. Okada and H. Fujimura (1990) Changes in cerebral white matter in a case of congenital muscular dystrophy (non-Fukuyama type). *Neuropediatrics*, 21: 183–186.
- Toda, T., M. Segawa, Y. Nomura, I. Nonaka, K. Masuda, T. Ishiara, M. Suzuki, I. Tomita, Y. Origuchi, K. Ohno, N. Misugi, Y. Sasaki, K. Takada, M. Kawai, K. Otani, T. Murukami, K. Saito, Y. Fukuyama, T. Shimizu, I. Kanazawa and Y. Nakamura (1993) Localization of a gene for Fukuyama type congenital muscular dystrophy to chromosome 9q31-33. *Nat. Genet.*, 5: 283.
- Topaloğlu, H., G. Kale, D. Yalnizoğlu, A.H. Taşdemir, A. Karaduman, M. Topçu and E. Kotiloğlu (1994) Analysis of “pure” congenital muscular dystrophies in thirty-eight cases. How different is the classical type 1 from the occidental type cerebromuscular dystrophy? *Neuropediatrics*, 25: 94–100.
- Towfighi, J., J.W. Sassani, K. Suzuki and R.L. Ladda (1984) Cerebro-ocular dysplasia-muscular dystrophy (COD-MD) syndrome. *Acta Neuropathol. (Berl.)*, 65: 110–123.
- Vassella, F., M. Mumenthaler and E. Rossi (1970) Congenital muscular dystrophy. In: J.N. Walton, N. Canal and G. Scarlato (Eds.), *Muscle Disease, Proc. Int. Cong.*, Milan, May 19–21, 1969, ICS 199, Excerpta Medica, Amsterdam, pp. 620–623.
- Yoshioka, M., S. Kuroki and H. Mizue (1987) Congenital muscular dystrophy of non-Fukuyama type with characteristic CT images. *Brain Dev.*, 9: 316–318.