Cortical Dysplasia in Congenital Muscular Dystrophy with Central Nervous System Involvement (Fukuyama Type)

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Abstract. We report five cases of congenital muscular dystrophy with central nervous system involvement of the Fukuyama type (FCMD) in which cerebral cortical dysplasia was not uniform even in the same brain. We have categorized the dysplasia into three major patterns, each with a predictable topography despite individual variations. Cerebellar micropolygyria was localized to the dorsal halves of each hemisphere. Aberrant fascicles of myelinated nerve fibers, closely associated with micropolygyria, were found in the subarachnoid space of the dorsal cerebellar surface in all but one case. We discuss the characteristics of the cortical dysplasia of FCMD, particularly in relation to that of Walker's lissencephaly, pathogenesis, and the relationship between lesions of the central nervous system and skeletal muscle.

Key Words: Muscular dystrophy, congenital; Dysplasia, cerebral cortical; Mircopolygyria.

INTRODUCTION

Congenital muscular dystrophy with central nervous system involvement of the Fukuyama type (FCMD) was described in 1960 (1). More than 200 patients have been recognized clinically in Japan where the disease appears to be more common (2). Patients manifest generalized muscular weakness and hypotonia from early infancy and most are unable to walk without support. All are mentally retarded and some have seizures, abnormal electroencephalograms (EEG) and abnormal computed tomograms (CT). Structural muscle abnormalities are similar to those of the Duchenne type of muscular dystrophy (3). Fukuyama et al (2) reviewed the neuropathological findings in 24 autopsied cases from the Japanese literature and concluded that brain malformation in patients with FCMD include cerebral and cerebellar micropolygyria, fibroglial proliferation in the leptomeninges, hydrocephalus, focal interhemispheric fusion, hypoplasia of the corticospinal tracts and various other anomalies. This is particularly true of the gross appearance of the cerebral cortex, ranging from lissencephalic appearance in the extreme cases (4, 5, 6) to abundant convolutions with granular surfaces (7, 8). Histologically, micropolygyria is a common feature, but different types of cortical dysplasia, such as verrucose dysplasia with otherwise normal cortical structure, were occasionally observed (8). We report five cases of FCMD in which the brain anomalies include the above mentioned findings as well as some additional ones. Aberrant fascicles coursing over the cerebellum were found in all the cases but one, though they were described previously in two cases merely as an ectopic accumulation of myelinated fibers (9, 10). The purpose of this report is to describe and illustrate the topography and cytoarchitec-
<table>
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<tr>
<th>Patient</th>
<th>1*</th>
<th>2*</th>
<th>3</th>
<th>4</th>
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<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
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<tr>
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<td>6 yr</td>
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<td>11 yr</td>
</tr>
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<tr>
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<td>2 yr</td>
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<tr>
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<td>No head support</td>
<td>No head support</td>
<td>Sat alone; no walking</td>
<td>Sat alone; crawling</td>
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<td>i ×, Febrile</td>
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<td>Sudden death</td>
<td>Cataract, right eye</td>
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Abbreviations: mo, months; ×, times; yr, years.

* Patients 1 and 2 have been reported (28) and were included in Fukuyama's report (2).
tural characteristics of the cerebral cortical dysplasia, and to clarify the nature of the aberrant fibers of the cerebellum.

MATERIALS AND METHODS

The brains of five patients between the ages of two and 11 years with clinical features of FCMD were examined (Table 1). Parental consanguinity did not exist in any of the cases. Patient 2 was a sporadic case, however there were affected siblings in the other cases. A marked delay in motor development and generalized hypotonia had been present since infancy in all the cases. Muscle wasting was diffuse and included the facial musculature and pseudohypertrophy of the calf muscles. All of the patients were mentally retarded, either severely (Patients 1, 2, 3) or moderately (Patients 4, 5). Patients 4 and 5 could form some sentences and could also sit unaided. None of the patients could walk without support. Muscle specimens obtained by biopsy or at autopsy revealed an extensive degeneration of muscle fibers with interstitial fibrosis. Contractures of the proximal and distal joints, and kyphoscoliosis of various degree were recorded since early infancy. Serum creatine kinase levels were elevated, but were not as high as reported among Duchenne muscular dystrophy patients. The cause of death was bronchopneumonia in all patients except for one who died suddenly of unknown causes. Congenital cataract of the right eye was recorded in Patient 2.

Formalin-fixed brains were sectioned in serial coronal slices about 1 cm in thickness. Paraffin sections obtained from at least five different levels of each hemisphere (anterior frontal, head of the caudate nucleus, lenticular nucleus, posterior thalamus, and occipital lobe) were used for cytoarchitectural study. These sections were stained with hematoxylin and eosin (H&E) and by the luxol fast blue (Klüver-Barrera) and Holzer methods. In addition to these stains, as immunohistochemical stain for glial fibrillary acidic protein (GFAP) (commercially available from DAKO Co. Ltd) was applied to several sections to evaluate glial proliferation. Serial sections from small tissue blocks of the cerebellum were reconstructed to study aberrant fascicles in the cerebellum.

RESULTS

Macroscopic Findings (Figure 1)

Brain weight was normal for the age of each patient (Table 2). Extensive areas with a smooth cortical surface in the cerebral hemispheres were present in four brains. These smooth foci involved the temporal and parieto-occipital lobes in various degrees (Patients 1–4). In the brain of Patient 5, smooth-surfaced areas were restricted to small foci in the vicinity of the occipital poles. The primary sulci (central, calcarine, parieto-occipital and cingulate) were evident in all brains. Away from the smooth-surfaced areas, the secondary sulci were shallow, and the gyrical surfaces had

<table>
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<th>TABLE 2</th>
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<tr>
<td>Brain Weights in Grams (g) of FCMD Patients Compared with Mean Values of Age-Matched Controls*</td>
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<table>
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<th>Patient (age)</th>
<th>Brain weight</th>
<th>Control*</th>
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<tr>
<td>1 (1 yr 11 mo)</td>
<td>1,140 g</td>
<td>982.8 g</td>
</tr>
<tr>
<td>2 (2 yr)</td>
<td>1,060 g</td>
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</tr>
<tr>
<td>3 (6 yr)</td>
<td>1,100 g</td>
<td>1,254.7 g</td>
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<td>4 (10 yr)</td>
<td>1,175 g</td>
<td>1,254.7 g</td>
</tr>
<tr>
<td>5 (11 yr)</td>
<td>1,460 g</td>
<td>1,241.6 g</td>
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* From Hoshi (Reference 29).
Abbreviations: mo, months; yr, years.

Fig. 1. Gross appearances of the brains. A–E: Lateral views of the brains. Cloudy, thickened leptomeninges over the frontal lobes are present in some cases. A, Patient 1; B, Patient 2; C, Patient 3; D, Patient 4; E, Patient 5; F, a coronal section of the brain of Patient 1 showing a focal fusion of the medial surfaces of the hemispheres. Similar findings were also found in the frontal lobes in Patients 2 and 5.

A coarse, granular appearance due to the presence of many small protuberances ("brain warts").

The leptomeninges were often thickened and adherent to the cerebral surface. Focal fusions of cortical gray matter (Fig. 1F) were present on the medial aspects of the frontal lobes in three cases (Patients 1, 2, 5).

The basal ganglia, thalamic nuclei and hippocampal gyri were macroscopically normal. Marked ventricular dilatation was present in the brain of Patient 3, and to a lesser degree in Patients 1 and 2. The olfactory bulbs and optic nerves were normal. An enlarged cavum septi pellucidi was present in Patients 1 and 2, but otherwise
there were no abnormalities of the midline structures such as the corpus callosum, anterior commissure, or massa intermedia.

In the cerebellum, smooth-surfaced areas in the dorsal aspects of the hemispheres were diffuse in two cases (Patients 2, 3), and localized to the superior semilunar lobules in the other three cases (Patients 1, 4, 5). Aberrant fascicles of myelinated fibers were found in the subarachnoid space in all brains except that of Patient 2. The folia of the ventral aspect of the cerebellum were relatively spared.

Cerebral Micropolygyria

Histological examination of the cerebral cortex revealed extensive cortical dysplasia similar to micropolygyria in all of the brains. The distribution of cortical dysplasia was almost symmetrical, but its patterns were different from site to site even in the same brain. The cortical dysplasias were categorized as three patterns, referred to as types 1, 2, and 3.

Type 1 dysplasia (Fig. 2A) was characterized by the presence of superficial cellular nodules, called verrucose dysplasia of the superficial and intracortical types (11). In these nodules, the molecular layer was absent and cellular layers appeared to be extruded to the surface. Otherwise cortical neurons were normally differentiated into six layers. Excessive folding of cellular layers without sulcus formation was observed, particularly at the bottom of the secondary sulci. Type 1 dysplasia was chiefly observed on the medial aspect of the occipital lobe and on the lateral surface of the temporal lobe.

Type 2 dysplasia (Fig. 2B) is a common type of cerebral micropolygyria composed of two distinctive layers; the molecular layer of a single, thick, cellular layer with excessive folds. Within the cellular layers there were numerous, irregular microsulci. Neuronal orientation was irregular and laminar differentiation was unclear. This
pattern was different from the four-layered type of micropolygyria. The superficial layer occasionally contained myelinated fibers, but usually not as many as in type 3 dysplasia. Type 2 dysplasia was chiefly observed in the frontal and parietal lobes. Type 3 dysplasia was most consistently found in the cortical areas which had smooth surfaces macroscopically. There were four distinctive layers (Fig. 2C): a) the
superficial layer which contained myelinated fibers obscuring the molecular layer; b) a thick cellular layer in which neurons were disorganized and occasionally aggregated and in which microsulci were not evident; c) a cell-sparse layer in which a large number of myelinated fibers were present; and d) an irregular neuronal arrangement. Narrow bundles of myelinated fibers arising from the underlying white matter were scattered in the fourth layer. Individual neurons appeared normal in spite of the severely altered cytoarchitecture. In all three types, the border between the cortex and white matter was clear and subcortical ectopic neurons were absent.

Proliferation of GFAP-positive glial cells in the superficial layer of the cerebral cortex was particularly evident in foci with types 2 and 3 dysplasia. The fibrous glial tissue often obliterated the subarachnoid space and surrounded leptomeningeal vessels. Glial proliferation did not occur in the deeper cortical layers except for perivascular areas in microsulci.

The topographical distribution of the three major types of cortical dysplasia is illustrated in Figure 3. Hippocampal gyri were spared in all cases, but cingulate gyri, insular cortex and cortex adjacent to the central and calcarine fissures showed abnormal cortical structure in varying degrees.

Cerebellar Micropolgyria and Aberrant Fascicles of Myelinated Nerve Fibers

Cerebellar micropolygyria was consistently found in the areas which were smooth on macroscopic examination (Fig. 4). In the malformed regions, there was extensive obliteration of the fissures. The cortical dysplasia was characterized by numerous small zones of the molecular and granular layers which were irregularly intermixed with each other. Purkinje cells were preferentially scattered in the borders between these two layers, occasionally associated with some myelinated fibers. Lobules adjacent to the micropolygyria were also anomalous particularly in the vicinity of the
obliterated fissures. Occasionally, abundant thin-walled blood vessels with a relatively large caliber were seen in the white matter underlying the micropolygyric cortex, and dense fibrillary gliosis was noted around such vessels. There was no significant increase of GFAP-positive cells in the superficial layer of the cerebellar cortical dysplasia in contrast with that of the cerebrum.

Aberrant fascicles on the cerebellar surface were found in four cases on gross inspection as mentioned above (Fig. 5A, B). A reconstructive study with serial histological sections revealed that these fascicles were closely connected with micropolygyric cortex. Some of them originated from the pontine tegmentum near the root of the trochlear nerve and terminated in micropolygyric cortex in the superior semilunar lobules through the subarachnoid space (Fig. 6A). Others arose from the white matter in the proximal lobules of the same hemisphere and also terminated in micropolygyric cortex (Fig. 6B). Histologically, these fascicles consisted of several bundles of myelinated nerve fibers often surrounded by fibrous glial tissue (Fig. 7). The presence of oligodendrocytes and GFAP-positive cells in these fascicles confirmed that they were of central nervous system derivation. No nerve cells were detected in these fascicles. They were usually separate from the cerebellar parenchyma, and occasionally adherent to the underlying micropolygyric cortex (Figs. 6C, 8).

In addition to the cortical dysplasia, there were some structural changes in other portions of the central nervous system. Myelin pallor in the centrum semiovale was noted in two cases (Patients 1, 2). In four cases (Patients 1, 2, 4, 5) there was a mild fibrillary gliosis in the cerebral white matter, even though no loss of myelin was found in the brains of Patients 4 and 5. A remarkable hypoplasia of the corticospinal tracts was noted in Patients 2 and 3, and to a lesser degree in the others. Abnormal
longitudinal and transverse fiber bundles were often found in the pons and medulla oblongata.

No heterotopic nodules of gray matter were found in periventricular portions of the white matter. The basal ganglia, thalamic nuclei and the deep cerebellar nuclei were normal. The contour and position of the inferior olivary nuclei were also normal.

DISCUSSION

The brain malformations in these five patients include the cerebral and cerebellar cortical dysplasias with considerable individual variations as previously reported (3, 9). The cytoarchitectural abnormalities may be grouped into three predominant types. All three types were observed in every brain examined except for that of Patient 2, and each type had a predictable topography. Verrucose dysplasia, characteristically found in type I dysplasia, has been described in various kinds of cerebral micropolygyria (11, 12, 13). Dvorak et al (14) observed morphologic changes similar to verrucose dysplasia in newborn rats after inducing focal aseptic necrosis in the superficial regions of the cerebral cortex. Similar necrotic lesions in the deep cortical
Fig. 7. Microphotograph of an aberrant fascicle (Patient 5) which consists of myelinated nerve fibers surrounded by glial tissue and located in the subarachnoid space, usually apart from the cerebellar parenchyma. Luxol fast blue (Klüver-Barrera) and H&E. ×192.

layers produced atypical micropolygyria with microsulcus formation. Therefore, type 1 cortical dysplasia may be a milder variety of cerebral micropolygyria. Type 2 cortical dysplasia apparently belongs in micropolygyria but is different from the four-layered "classical" type. This is a common type of micropolygyria in the FCMD patients. Type 3 dysplasia consists of four distinctive layers, in which the smooth surface superficially resembles lissencephaly. In lissencephaly, cortical neurons in the upper cellular layer usually have a radial arrangement, while type 3 dysplasia neurons are severely disorganized. Therefore, we consider type 3 dysplasia also a variant of micropolygyria despite its smooth surfaces grossly.

The different dysplastic cortical patterns may reflect differences in the chronology and severity of the pathogenetic process. Cerebral micropolygyria, particularly the four-layered type, has been ascribed to a destructive process that affects cortical neurons after neuronal migration is completed, around the sixth intrauterine month (15, 16). However, even if this is true, the classical four-layered type, it does not seem to apply to all cases presented in this study. Other variants of micropolygyria, an earlier time of intrauterine life is considered, is the teratogenic period (17, 18). Subcortical ectopic neurons, which may indicate that the destructive process occurred before 16-20 weeks of gestation, the time of completion of neuronal migration (18) are absent in all of our cases. In FCMD, the causative agent may operate with various intensities for a protracted period around the time of the termination of neuronal migration. The bilateral and symmetrical distribution of the lesions in each dysplasia type suggests that they are influenced by intrinsic factors, such as special vascularization and different timing in cell differentiation. In micropolygyria, other than that seen in FCMD, the malformed cortices are often within the territory of the middle cerebral artery (15, 18, 19). In the cases presented here, the topographic distribution of the cerebral cortical dysplasia does not seem to correlate with the territories of the major cerebral arteries or with their boundary zones.

From a clinicopathological viewpoint, a close correlation is suggested between the degree of the malformation and that of mental retardation: in patients with severe retardation (Patients 1-3), type 3 dysplasia was more extensive than in Patients 4 and 5 (Table 1, Fig. 3); a marked hydrocephalus was present in Patient 3; and abnormal myelination of the cerebral white matter in Patients 1 and 2.
Another example of an unusual dysplasia with a smooth cortical surface has been described in Walker's "lissencephaly" (20, 21) in which cortical neurons are arranged in irregular groups, sometimes separated by less cellular zones, and individual neurons often show an abnormal orientation. This feature suggests a variant form of micropolygyria as interpreted by Friede (22). There are some morphological resemblances between Walker's "lissencephaly" and FCMD. These similar features include: obliteration of the subarachnoid space by fibroglial tissue; extensive cortical malformations of the cerebrum and cerebellum with relative preservation of the lower portion of the cerebellum; normal architecture of the basal ganglia and inferior olivary nuclei; absence of periventricular heterotopic nodules of gray matter; and remarkable hypoplasia of the pyramidal tracts. A fetal infection of the brain and eyes has been suggested as the cause of this malformation (21). Some FCMD patients were associated with congenital cataract (3, 4, and 5, and Patient 2 in this study); the brain abnormalities were rather profound among these FCMD patients and similar to Walker's malformation.

According to some authors (4, 23), fibroglial and vascular proliferation in the leptomeninges suggests an intrauterine infection as a causative factor for the cortical dysplasia in FCMD. This hypothesis, as extensively discussed by Kamoshita (23), explains the lesions of both the central nervous system and skeletal muscles as sequelae of intrauterine meningoencephalitis and polymyositis, respectively. We consider that fibroglial proliferation itself may imply not only infection, but also any destructive process in late fetal life. Furthermore, the following features of the disease make it difficult to explain the etiology of FCMD solely on an infectious basis: a) there is strong evidence for an autosomal recessive inheritance (24); b) muscle changes are progressive throughout postnatal life and are devoid of inflammation (3); c) serological investigations of conventional viruses and mycoplasmas in FCMD patients have yielded negative results (24, 25).
Cerebellar micropolygyria was also present in all the cases of this report. It tends to be localized on the dorsal surfaces, particularly the superior semilunar lobules, where the topography is unrelated to the territories of the cerebellar arteries. Aberrant myelinated fibers on the cerebellar surface have been described previously in two cases of FCMD (9, 10). The present study revealed that most of these fascicles establish connections between the micropolygyric cerebellar cortex and either the pontine tegmentum or the white matter of another lobule in the same hemisphere. Although it remains obscure how these fascicles develop, they may be interpreted as ectopic white matter which is extruded from the malformed cortex into the subarachnoid space possibly due to focal destruction of the glial limiting membrane in the pia mater. The development of aberrant fascicles presumably follows the development of cerebellar folia by the twentieth fetal week, because the fascicles often override many normal folia. This may approximately coincide with the timing of cerebellar micropolygyria in the late stage of the second trimester (14, 26).

The final question is whether the abnormalities in the central nervous system may account for the muscle changes. The pyramidal tracts are hypoplastic in all the cases. Pyramidal tract disease may express itself as a type 2 fiber atrophy (27), but not as a dystrophic change in muscle. The anterior horn cells appear normal in shape and in number at various levels of the spinal cord. The anterior and posterior spinal roots contain myelinated fibers normal in number and size (28). The muscle changes are, in contrast, progressive and consist of small-caliber fibers with marked variations in myofiber size, connective tissue proliferation, and scattered necrotic and regenerating fibers (3). There are no qualitative differences in the muscle changes between FCMD and Duchenne type muscular dystrophy and marked fibrosis is visible in the early stage of FCMD. In summary, the skeletal muscle changes are essentially dystrophic and there is no evidence for a direct influence of the central nervous system. Although the etiology of this peculiar disease is obscure, it seems reasonable to postulate that a single pleiotropic gene, manifesting itself a metabolic error, may account for the lesions in both the skeletal muscles and in the central nervous system.

ACKNOWLEDGMENTS

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