Clinical features, particularly those of the central nervous system, of patients with Becker's muscular dystrophy, including autopsied cases

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Abstract

There are no detailed reports about the clinical and pathological findings in the central nervous system (CNS) of patients with Becker's muscular dystrophy (BMD), although dysfunctions of the skeletal and cardiac muscles are well known in BMD. Since dystrophin is present in the CNS, and usual medical treatment is often influenced by CNS manifestations in patients, we studied the clinical and pathological features of BMD, with particular focus on the CNS manifestations, and also examined the relationships of these features with skeletal and cardiac muscle dysfunctions. We examined eight BMD patients aged 24-77 years who were admitted to our hospital, and six autopsied BMD patients aged 39-58 years. In addition to family histories of the patients, clinical findings, and disease progression, BMD was diagnosed based on the presence of dystrophin revealed by immunohistochemical examination and examination of the dystrophin gene. Brain computed tomography (CT), magnetic resonance imaging (MRI), and CNS pathohistology were also performed. Gene analyses by multiplex PCR revealed that exons 3-4, 3-6, 12-19, 45-47,45-49, and 45-52 were deleted; all the deletions occurred in hot spots in the dystrophin gene. With regard to the clinical CNS manifestations of BMD, 2 of the 14 patients experienced hallucinations, but there was no patient with severe mental retardation. Brain CT and MRI scans revealed various grades of mild atrophy of the front-parietal lobe for all the patients. Low-magnification microscopy images of the brain of three autopsied patients with mild BMD showed that the gyri of the brain were separated, suggesting brain atrophy. The nerve cells of the frontal lobe, however, seemed to be unaffected histologically. These results show that there are mild abnormalities in the CNS of BMD patients. It is well known that BMD patients demonstrate different levels of skeletal and cardiac muscle dysfunctions. In the current study as well, the BMD patients demonstrated CNS abnormalities, although these abnormalities were mild compared to the skeletal and cardiac muscle dysfunctions.

Key Words: Angiotensin II receptor blocker, ARB, UPDRS, PDQ-39, SDS, HAD, and SUBI

Introduction

We previously reported that the dysfunction of skeletal muscles, the myocardium or the central nervous system was present in woman carriers of Duchenne-type muscular dystrophy [1]. This suggested that a pathomechanism which was similar to that found in patients with Duchenne-type disease was present in woman carriers. We histologically examined the central nervous system in addition to skeletal muscle and the myocardium in patients with Becker muscular dystrophy which has dystrophinopathy similar to Duchenne muscular dystrophy.

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Table 1. Results of the clinical examinations

Case No.		Age	Deleted exons	Staining of dystrophin	Duration of hospitalization (years)	Clinical manifestation of the CNS
Outpatient	1	24	3-6	nd*	—	—
	2	37	nd	patchy	—	Previous cerebral hemorrhage
	3	42	45-52	nd	—	Asymptomatic syphilis
	4	46	45-47	nd	—	Hallucination
Inpatient	1	57	45–49	nd	27	—
	2	71	45-47	nd	17	—
	3	75	45-47	nd	27	—
	4	77	45-47	nd	30	—
Autopsied case	1	50	3,4	nd	4	—
	2	* 52	nd	nd	14	Vegetative state
	3	39	nd	patchy	12	—
	4	47	12-19	nd	6	—
	5	53	3-6	nd	26	—
	6	58	3,4	nd	20	Hallucination

* Diagnosed by type of inheritance
* nd = not detected

Subjects and methods

The subjects were eight Becker-type patients currently hospitalized at Tokushima Hospital (age range, 24-77 years) and six Becker-type patients who had died at this hospital and had been autopsied (age range, 39-58 years old). Four patients died of respiratory failure, and two died of cardio-respiratory failure. The diagnosis of Becker-type muscular dystrophy was made following a search for the dystrophin immunohistochemistry of the muscle or the dystrophin gene as well as genotype, clinical examination / the course. In ten cases, dystrophin genetic screening was performed, and all the deletion sites were hot spots including exon3, 4, 3-6, 12-19, 45-47, 45-49, and 45-52 (table 1). A head CT, and a head MRI were carried out to examine the central nervous system. Furthermore, brain weight and the pathological characteristics of the brain were examined in the autopsy cases. Functional disorder degree of lower limbs, serum CK activity levels and expression of dystrophin by Western blot analysis of a muscle sample [2] were examined about the skeletal muscle function. Clinical manifestations, cardiothoracic ratio, plasma atrial natriuretic peptide (ANP) levels [3], and plasma brain-related natriuresis peptide (BNP) levels [4] were examined for cardiac activity.

Results

Clinical examination was performed on four Becker-type outpatients (24-46 years old) and four inpatients (57-77 years old, length of hospitalization, 17-30 years).Hallucination, old cerebral hemorrhage, and asymptomatic syphilis were present in the central nervous system as complications (table 1). There was no case showing clear retardation of mental development. Head MRI findings of four outpatients demonstrated that minor atrophy was present in three front parietal lobes (figure 1), and a hemosiderin deposition image of the localized was found in one right occipital lobe cortex. Atrophy of the frontal lobe was present in three of the patients aged in their 70s in the head CT of four hospitalization cases (figure 2). Regarding the skeletal muscle function, the functional disorder degree of the lower limbs was 4-8. Serum CK activity level 131-3052 was

IU/L(normal <200). The dystrophin expression determined in two cases by Western blot analysis of the muscle sample was decreased to 23% and 12% (autopsy example) respectively (table 1). Regarding cardiac activity, the cardiothoracic ratio was 37.5-64.1% plasma ANP level 5.2-25.8 pg/ml (normal <43), and plasma BNP level 0.4-32.1 was pg/ml(normal <18.4). The skeletal muscle symptoms were remarkable, but heart symptoms and the symptoms of the central nervous system were not present or were slight if they did exist. Autopsies were performed on four patients who had died of cardio-respiratory failure and two patients who had died of respiratory failure. Age at onset was 5-16 years old, and the gait inability age was 15-35 years old. The length of hospitalization was 4-26 years. The cardiothoracic ratio spread to 52-54% in the cardio-respiratory failure group, but it was within normal limits in the respiratory failure group. The brain weight was 1250-1400g in the cardio-respiratory failure group, and was 970-1250g in the respiratory failure group; (table 2). Sulcus of the brain had spread in three cases and was visible using a loupe image (figure 3). The frontal plane was shown in one case, and expansion of the sulcus of the brain was confirmed. The nerve cell of the frontal lobe did not show any clear abnormality. Ischemic change was present in two cases with brain tissue.

Discussion

Skeletal muscle dysfunction and myocardial disorder [5] are well known in Becker-type muscular dystrophy patients. On the other hand, it has been reported that dystrophin is expressed [6] in the central nervous system in these patients and that mental symptoms [7] often appear, causing an impediment to daily life. However, there have been no reports giving pathological findings on the central nervous system. We made a clinical examination and gave pathological findings about the central nervous system mainly. Mental symptoms such as hallucination were very apparent in the Becker-type muscular dystrophy patients. Cerebral atrophy was present in head MRI and CT scans.We previously examined the central nerve dysfunction of Duchenne-type patients in whom intelligence was highly affected and reported that primary central nerve dysfunction was present in these cases [8]. In these patients, amyloid-like conglobation and an allopatric nerve cell in the white matter were very noticeable in the brain pathological findings. Brain atrophy was found in head MRI and CT scans, mainly on the frontal lobe in the Becker-type patients examined in the present study. Therefore we examined the brain pathological findings of the frontal lobe. There were no clear abnormal findings, but a more detailed search will be necessary in future. There is already a report about the connection with deletion sites of the dystrophin gene and the central nerve dysfunction. It is stated that retardation of mental development is present in cases with mutation in 3' sides in patients with Duchenne-type muscular dystrophy. Our cases did not show retardation of mental development, but there were patients with hallucination, whose dystrophin gene deletion sites were exons 3-4 and exons 45-49. The defect sites of the gene are both hot spots, andwe consider it unlikely that these mutations caused the mental disorders in our cases. The dystrophin expression of the muscle sample was greatly decreased to 23% and 12%. There was front parietal lobe atrophy in MRI in the former, in addition to hallucination, and severe brain atrophy findings were discovered by autopsy in the latter. The relation between brain expression of dystrophin in Becker-type patients and central nerve dysfunction will need more examination in future. In Becker-type patients, the dysfunctions in the skeletal and cardiac muscles are more minor than in Duchenne-type patients. We reported that central nerve dysfunction in Becker-type patients was also more minor than in Duchenne-type patients.

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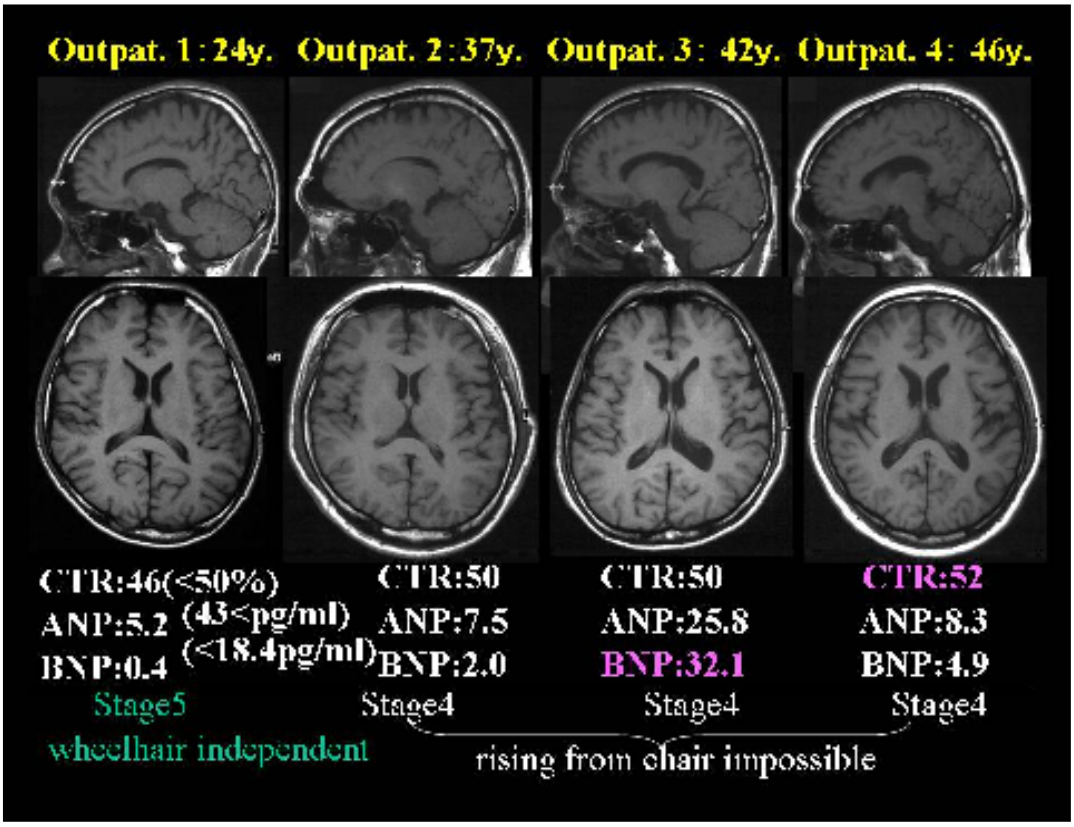

Figure 1. MRI findings.We observed no association between the MRI findings and the muscle function test.

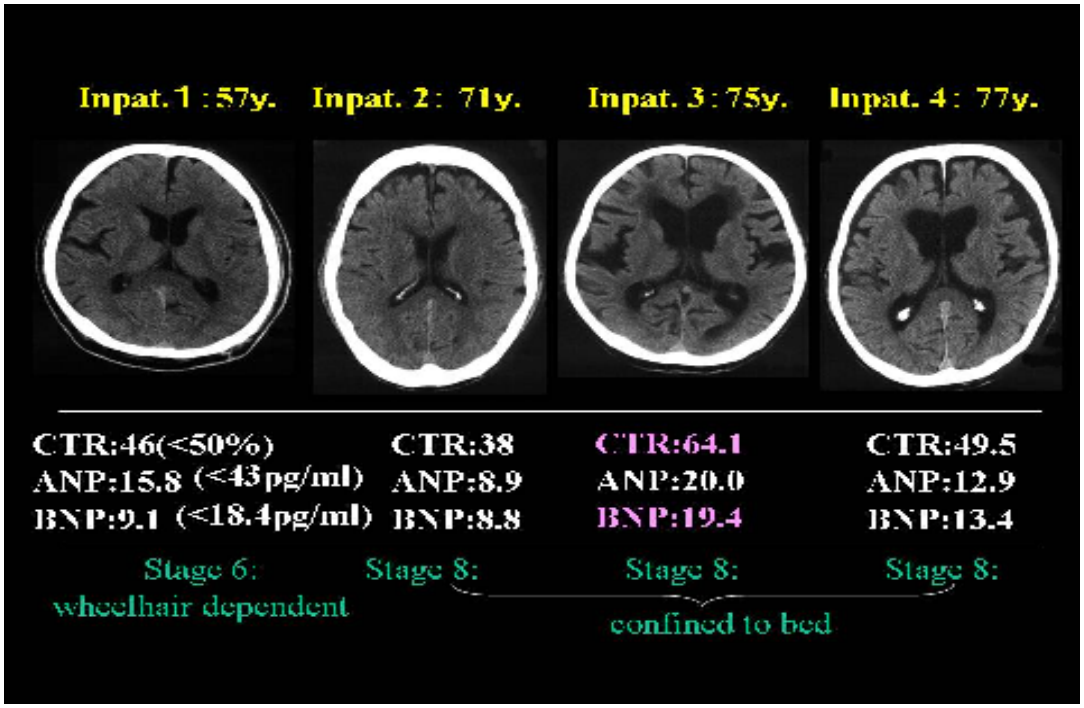

Figure 2. CT findings.We observed no association between the CT findings and the muscle function test.

Table 2. Summary of clinical findings of the CNS (frontal lobes)

Autopsied case	Case 1: 50 y	Case 2: 52 y	Case 3: 39 y	Case 4: 47 y	Case 5: 53 y	Case 6: 58 y
Manifestation of CNS	(−)	Vegetative state	(−)	(−)	(−)	Hallucination
Cause of death	Respiratory failure	Respiratory failure	Cardiac failure	Cardiac failure	Respiratory failure	Respiratory failure
Brain weight	1200 g	970 g	1400 g	1250 g	1250 g	1200 g
Macroscopic findings	nd	Cerebellar atrophy, thinner gray matter	nil	nd	nd	Cerebellar atrophy
Low magnification microscopic images	nd	nd	Gyri were separated	nd	Gyri were separated	Gyri were separated
Ischemic changes	(−)	(+)	(+)	(−)	(−)	(−)
Ectopic nerve cells in white matter	(−)	(−)	(−)	(−)	(−)	(−)

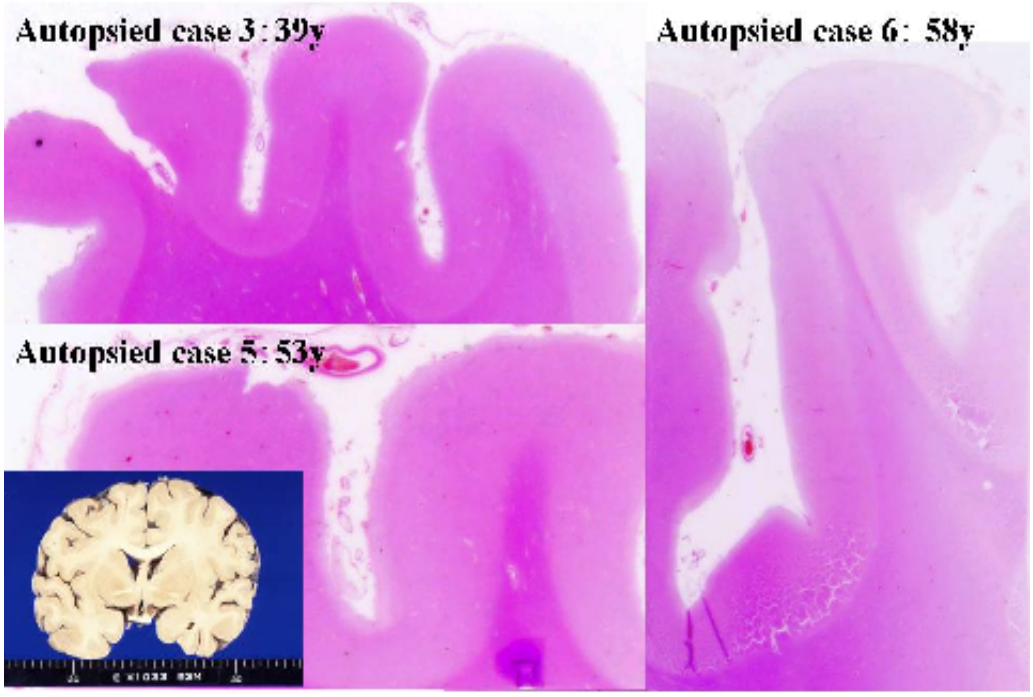

Figure 3. Low-magnification microscopy images of the frontal lobe. The frontal section of the case-5 patient brain(Inset).
The gyri of the brain were separated, which is suggestive of brain atroph

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