Risk Factors for Cerebral Infarction in Duchenne Muscular Dystrophy: Review With our 2 Cases

Fumihito Nozaki, MD, Takashi Kusunoki, MD, PhD, Tomohiro Kumada, MD, PhD, Minoru Shibata, MD, and Tatsuya Fujii, MD, PhD

Background: Although the incidence of cerebral infarction is higher in Duchenne muscular dystrophy (.75 per 100) than in the general population (7.5-11.4 per 100 000), only 18 cases have been reported, and prevention and management guidelines for infarction in this disorder remain lacking. *Patients and Methods:* We encountered 2 cases of Duchenne muscular dystrophy with cerebral infarction. To clarify risk factors for such infarction in Duchenne muscular dystrophy, we reviewed 20 cases, including our 2 patients. *Results:* Age at onset of infarction ranged from 4 to 31 years (n = 19). Most patients were 16-21 years old (14 of 19; 73.7%). Eighteen patients (90%) had dilated cardiomyopathy (DCM), showing a higher frequency than in the age-matched general Duchenne muscular dystrophy population. Left ventricular ejection fraction (LVEF) ranged from 10.2% to 42% (median, 20%; n = 9). Detectable cardiac thrombus and atrial fibrillation were rare (2 of 17; 11.8%, and 1 of 17; 5.9%, respectively). *Conclusions:* Presence of DCM with low LVEF seems to be the strongest risk factor for cerebral infarction in Duchenne muscular dystrophy.

Key Words: Duchenne muscular dystrophy—cerebral infarction—dilated cardiomyopathy—ejection fraction

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked progressive myopathy caused by mutations within the dystrophin gene. Although advancement of management such as mechanical ventilation techniques and therapeutic interventions for cardiomyopathy has improved life expectancy for these individuals, other complications including cerebral infarction occasionally arise. The incidence of cerebral infarction in DMD is reported to be .75 per 100, which is 100 times higher compared to the incidence of ischemic stroke in general young male adults (7.5-11.4 per 100,000).[1,2] However, no guideline recommendations have been established for the prevention and management of cerebral infarction in DMD patients. Here we present 2 cases of DMD with cerebral infarction that we encountered, and review those cases and the 18 other reported cases to clarify the features of DMD patients who develop cerebral infarction.

Patients and Methods

Patient 1

A 19-year-old DMD patient with dilated cardiomyopathy (DCM) was referred to us with amnesia, disorientation, and somnolence that were identified on awakening in the morning. He showed deletion of exons 48-50 in the dystrophin gene and was nonambulatory, but did not have respiratory failure necessitating a ventilator. The family history, including of vascular diseases, was unremarkable. He had been on glucocorticoid therapy (prednisolone 5 mg/kg/day, given twice a week) since he was 8 years old. Therapeutic intervention for cardiomyopathy using angiotensin-converting enzyme inhibitor had been initiated at 11 years old. At 19 years old, left ventricular ejection fraction (LVEF) was 38% and the blood concentration of brain natriuretic peptide was 46.6 pg/mL (normal, less than 18.4 pg/mL). No valvular heart disease or septal defects were evident.

From the Department of Pediatrics, Shiga Medical Center for Children, Moriyama, Japan.

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Address correspondence to Fumihito Nozaki, MD, Department of Pediatrics, Shiga Medical Center for Children, 5-7-30 Moriyama, Moriyama City, Shiga 524-0022, Japan. E-mail: nozaki-kgw@umin.ac.jp.

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Cerebral magnetic resonance imaging (MRI) demonstrated bilateral paramedian thalamic infarction (Fig. 1A). Results from magnetic resonance angiography were unremarkable, indicating that the infarction had occurred in the territory of a penetrating artery from the paramedian thalamic artery. Echocardiography revealed no thrombus formation (transesophageal echocardiography could not be performed). No arrhythmia was evident, including atrial fibrillation. Serum level of thrombin-antithrombin complex was 4.7 ng/mL (normal, <3.0 ng/mL), and the concentration of D-dimer was less than .5 μg/mL (normal, <1.0 μg/mL). Abnormalities of blood constituents indicating dehydration or increased blood viscosity (elevated hematocrit or fibrinogen) [3] were not identified. Antiplatelet therapy with aspirin was initiated and symptoms completely resolved within 3 weeks. Cerebral infarction did not recur during the following 2 years with aspirin for secondary prophylaxis, but he died of cardiac failure due to severe arrhythmia at 21 years old.

Patient 2

A 20-year-old DMD patient with DCM was referred to us complaining of paresthesia in the right fingers and right homonymous hemianopsia. He showed deletion of exons 45-52 in the dystrophin gene. The family history, including of vascular diseases, was unremarkable. He had been on glucocorticoid therapy (prednisolone .5 mg/kg/day, every other day) since he was 5 years old. Therapeutic intervention for cardiomyopathy with angiotensin-converting enzyme inhibitor had been initiated at 14 years old. At 20 years old, LVEF was 40% and blood level of brain natriuretic peptide was 57.5 pg/mL. No valvular heart diseases or septal defects were evident.

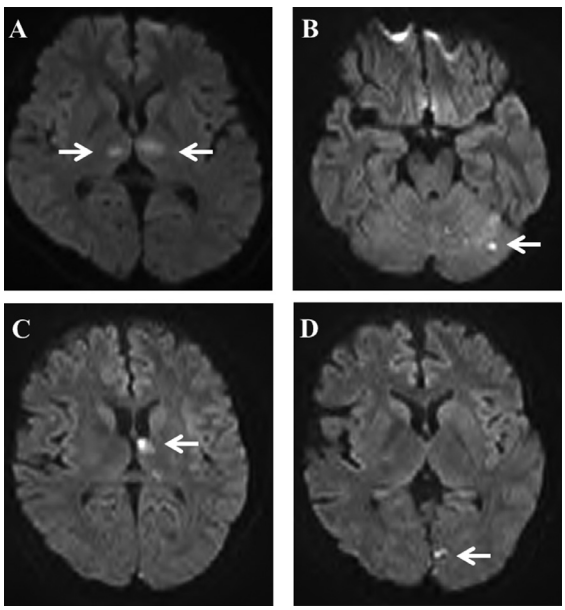

Figure 1. *Diffusion-weighted imaging of the brain. Bilateral paramedian thalamic infarction is evident in Patient 1 (A). Multiple infarctions in the left cerebellar hemisphere (B), thalamus (C), and occipital lobe (D) are evident in Patient 2. White arrows indicate regions of cerebral infarction in both patients.*

Cerebral MRI demonstrated multiple infarctions in the left cerebellar hemisphere, thalamus, and occipital lobe (Fig. 1B-D). Results from magnetic resonance angiography were unremarkable, indicating that the infarctions had occurred in the territory of penetrating arteries from the left posterior cerebral and superior cerebellar arteries. Echocardiography (we could not perform transesophageal echocardiography) revealed no thrombus formation. No arrhythmia was evident, including atrial fibrillation. Serum level of TAT was 2.1 ng/mL and concentration of D-dimer was .5 μg/mL. No abnormalities of blood constituents indicating dehydration or increased blood viscosity were identified. Antiplatelet therapy with aspirin was initiated and symptoms completely resolved within 2 weeks. Cerebral infarction did not recur during the following 2 years with aspirin for secondary prophylaxis.

Methods

The PubMed database was searched for articles using the keywords "*Duchenne muscular dystrophy*" and "*cerebral infarction*" or "*stroke*", identifying a total of 18 cases of DMD patients with cerebral infarction.[1,4-11] To clarify the risk factors for the infarction in Duchenne muscular dystrophy, we reviewed 20 cases including our 2 patients. All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, New York). To compare the prevalence of DCM between DMD patients with and without infarction, we used Pearson's chi-square test. Statistical significance was defined as $P < .01$.

Results

Tables 1 and 2 show the profile and the clinical features of 20 patients. Age at diagnosis of infarction ranged from 4 to 31 years (n = 19), with ages of individual cases described for 14 patients (range, 4-31 years; median, 18 years; interquartile range, 15-21 years). The cause of infarction in the 4-year-old boy might have been *Mycoplasma pneumoniae* infection, so exclusion of this patient resulted in an age range of 13-31 years (median, 19 years; interquartile range, 16-21 years). In the remaining 5 patients, ages at onset were described collectively, not individually (range, 16-20 years).[1] The majority of patients were thus 16-21 years old (14 of 19, 73.7%).

The infarction developed in a variety of vascular territories, including those of the middle cerebral, posterior cerebral, basilar, paramedian thalamic, and superior cerebellar arteries. Among these, the territory of the middle cerebral artery was the most common (15 patients; 75%, n = 20). The majority of patients (18 patients; 90%, n = 20) showed DCM, including all patients more than equal to 13 years old. Among the 2 patients without DCM, 1 patient had left ventricular hypertrophy, and the

Table 1. *Summary of 20 cases of DMD patients with cerebral infarction*

Patients	1 [1,6]	2 [1,6]	3 [1,6]	4 [1,6]	5 [1,6]	6 [1,6]
Age (y)	16-20 (individual ages not described in patients 1-5)					-
Vascular territory	MCA	MCA	MCA	MCA	MCA	MCA
Cardiac involvement	DCM	DCM	DCM	DCM	DCM	No cardiomyopathy
Left ventricular ejection fraction (%)	-	-	-	-	-	-
Cardiac thrombus	No	No	No	No	No	No
Arrhythmia	No	AF	No	VPC	No	No
Coagulation function	-	-	-	-	-	-
Glucocorticoid therapy	-	-	-	-	-	-
Other factors*	-	-	-	-	-	-
Treatment	-	-	-	-	-	-
Secondary prophylaxis	-	-	-	-	-	-

Patients	7 [4]	8 [4]	9 [4]	10 [4]	11 [5]	12 [6]
Age (y)	16	16	13	16	21	21
Vascular territory	MCA	MCA	Left hemisphere	MCA	MCA	MCA
Cardiac involvement	DCM	DCM	DCM	DCM	DCM	DCM
Left ventricular ejection fraction (%)	Reduced	42	-	Reduced	19	10.2
Cardiac thrombus	No	No	-	No	Yes	No
Arrhythmia	No	No	No	No	No	No
Coagulation function	Normal	Normal	-	-	Normal	TAT 9.7 ng/mL, D-dimer 1.41 μg/mL
Glucocorticoid therapy	-	-	-	-	-	-
Other factors*	-	-	-	-	-	-
Treatment	Thrombolysis Anticoagulation therapy	Thrombolysis	No	No	Anticoagulation therapy	Anticoagulation therapy
Secondary prophylaxis	-	Antiplatelet therapy	-	-	-	Anticoagulation therapy

Patients	13 [6]	14 [7]	15 [8]	16 [9]	17 [10]
Age (y)	26	4	17	13	31
Vascular territory	MCA	Basilar artery	Basilar artery and		
posterior cerebral artery	MCA	MCA			
Cardiac involvement	DCM	Left ventricular hypertrophy	DCM	DCM	DCM
Left ventricular ejection fraction (%)	10.3	-	15-20	35-40	20
Cardiac thrombus	No	-	No	-	Yes
Arrhythmia	VPC	-	-	-	No
Coagulation function	TAT 7.6 ng/mL, D-dimer† 252 ng/mL	-	-	-	-
Glucocorticoid therapy	-	-	-	-	-
Other factors*	-	-	-	-	-
Treatment	-	-	Anticoagulation therapy	-	Anticoagulation therapy
Secondary prophylaxis	-	-	-	-	-

Patients	18 [11]	19 (Our patient 1)	20 (Our patient 2)
Age (y)	20	19	20
Vascular territory	MCA	Paramedian thalamic artery	Posterior cerebral artery and superior cerebellar artery
Cardiac involvement	DCM	DCM	DCM
Left ventricular ejection fraction (%)	Reduced	38	40
Cardiac thrombus	No	No	No
Arrhythmia	No	No	No
Coagulation function	Normal	TAT 4.7 ng/mL, D-dimer <.5 μg/mL	TAT 2.1 ng/mL, D-dimer .5 μg/mL
Glucocorticoid therapy	-	Prednisolone 5mg/kg/day, twice a week	Prednisolone .5mg/kg/day, every other day
Other factors*	-	No	No
Treatment	Mechanical thrombectomy	Antiplatelet therapy	Antiplatelet therapy
Secondary prophylaxis	Anticoagulation therapy	Antiplatelet therapy	Antiplatelet therapy

Abbreviations: AF; atrial fibrillation, DCM; dilated cardiomyopathy, MCA; middle cerebral artery, TAT; thrombin-antithrombin complex, VPC; ventricular premature contraction.

*dehydration and/or increased blood viscosity, -; not described.

†Normal coagulation values: TAT; < 3.0 ng/mL, D-dimer; < 1.0 ug/mL in latex photometric immunoassay or <150 ng/mL in enzyme immunoassay.

remaining patient showed no echocardiographic abnormality. LVEF ranged from 10.2% to 42% (n = 9). In 2 patients, LVEF was 15%-20% and 35%-40%, respectively. Taking the highest values in these 2 patients, the median was 20% (interquartile range, 14.7%-40.0%). Cardiac thrombus was detected in only 2 patients (11.8%) among the 17 patients who underwent specific searches for cardiac thrombus. Arrhythmia was detected in 3 patients (17.6%) (ventricular premature contraction in 2, atrial fibrillation in 1) among the 17 patients tested for arrhythmia. Among the 8 patients tested for coagulation function, 3 patients (37.5%) displayed elevated concentrations of TAT (9.7 ng/mL, 7.6 ng/mL, and 4.7 ng/mL), 2 patients (25%) showed elevated levels of D-dimer (1.41 μg/mL (latex photometric immunoassay; normal, <1.0 μg/mL) and 252 ng/mL (enzyme immunoassay; normal, <150 ng/mL)), and 5 patients (62.5%) showed normal results. The use of glucocorticoid therapy was described only in our 2 cases. Other factors including dehydration and increased blood viscosity were described only in our 2 cases. Treatments for cerebral infarction in DMD patients varied, comprising anticoagulation therapy in 5 patients, antiplatelet therapy in 2 patients, thrombolysis in 2 patients, and mechanical thrombectomy in 1 patient (n = 9). For secondary prophylaxis, antiplatelet therapy was administered in 3 patients and anticoagulation therapy was given to 2 patients (n = 5).

Discussion

The incidence of cerebral infarction in DMD patients has been reported as .75 per 100 or 1 per 100 patients-years, roughly 100 times higher than that in the general young male adult population aged 18-44 years (7.5-11.4 per 100,000).[1,2,4] Prevention and early detection of cerebral infarction in DMD patients are thus crucially important. However, management guidelines are lacking for cerebral infarction in DMD patient.[4,12]

With this review, including our own cases, we tried to characterize the features of DMD patients who developed cerebral infarction, and thus clarify risk factors for infarction (Table 2). Except for 1 exceptionally young patient (4 years old) in whom the infarction could have been attributable to *Mycoplasma pneumoniae* infection,[7] ages at

Table 2. *Features of DMD patients with cerebral infarction*

Features (Number of Patients With Feature Described)	Findings in described cases, Including our 2 Patients
Age (n = 19)	Range: 4-31 y
	13-31 y, excluding a 4-year-old patient* (median, 19 y; interquartile range, 16-21 y; n = 13)
	16-20 y (individual ages not described; n = 5)
Vascular territories involved (n = 20)	Middle cerebral artery (n = 15)
	Basilar artery (n = 1)
	Basilar artery and posterior cerebral artery (n = 1)
	Left hemisphere (n = 1)
	Paramedian thalamic artery (n = 1)
	Posterior cerebral artery and superior cerebellar artery (n = 1)
Cardiac involvement (n = 20)	Dilated cardiomyopathy (n = 18)
	Left ventricular hypertrophy (n = 1)
	No cardiomyopathy (n = 1)
Left ventricular ejection fraction (n = 9)	10.2%-42% (median, 20%)
Cardiac thrombus (n = 17)	2 patients
Arrhythmia (n = 17)	Ventricular premature contraction (n = 2)
	Atrial fibrillation (n = 1)
Coagulation function (n = 8)	Normal (n = 5)
	Elevated level of TAT (n = 3)
	Elevated level of D-dimer (n = 2)
Glucocorticoid therapy (n = 2)	Prednisolone 5 mg/kg/day, twice a week (n = 1)
	Prednisolone .5 mg/kg/day, every other day (n = 1)
Dehydration and/or abnormalities of blood constituents leading to hyperviscosity (n = 2)	None
Treatment (n = 9)	Anticoagulation therapy (n = 5)
	Antiplatelet therapy (n = 2)
	Thrombolysis (n = 2)
	Mechanical thrombectomy (n = 1)
Secondary prophylaxis (n = 5)	Antiplatelet therapy (n = 3)
	Anticoagulation therapy (n=2)

Abbreviation: TAT, thrombin-antithrombin complex.
*Cause of infarction in this patient was possibly mycoplasma infection.

onset in the 13 patients with infarction for whom age was described ranged from 13 to 31 years (median, 19 years; interquartile range, 16-21 years). In the other 5 patients for whom individual ages were not described, the age range was 16-20 years. These data indicate that DMD patients from 16 to 21 years old are at high risk of cerebral infarction. In general, most DMD patients become nonambulatory by 13 years old. All but 1 patient in this study were more than equal to 13 years old at the time of infarction, indicating that a nonambulatory status might represent a risk factor for infarction. However, we do not have any evidence that nonambulation itself might have triggered the cerebral infarction.

The majority of patients (18 of 20; 90%) had DCM, and these patients showed an age range of 13-31 years. Nigro et al reported on the incidences of cardiomyopathy in 328 DMD patients: 0 among patients less than 10 years old (n = 105); 26 of 101 (25.7%) at 10-14 years old, 34 of 76 (44.7%) at 14-18 years old, and 33 of 46 (71.7%) at more than 18 years old.[13] We compared the incidence of DCM among patients more than equal to 14 years old between their DMD patients and the patients we identified. Each of our 16 patients more than equal to 14 years old had DCM (100%), compared to 67 of their 122 DMD patients (55%). The incidence of DCM was significantly higher in DMD patients with cerebral infarction ($P < .01$; Pearson's chi-square test), indicating that the presence of DCM represents a major risk factor for this infarction.

DCM causes a reduction in LVEF, in turn triggering thrombus formation. LVEF in patients with infarction ranged from 10.2% to 42% (median, 20%; n = 9). In the general population, stroke risk reportedly increases by 18% with every 5% decline in LVEF.[14] However, we do not know whether the incidence of infarction is higher in DMD patients than in the non-DMD population with the same degree of LVEF reduction. As the number of patients for whom LVEF was described was small, we could not estimate any LVEF threshold for the risk for the infarction in DMD patients with DCM.

Cardiac thrombus and arrhythmia (including atrial fibrillation) were rare in our survey, meaning that these 2 factors are not common causes of infarction in DMD patients. However, transesophageal echocardiography, which offers superior detection of cardiac thrombus compared to transthoracic echocardiography,[3] was not performed in most DMD patients with cerebral infarction. Only 2 patients were evaluated by transesophageal echocardiography, and no thrombus was evident in those cases.[4,11] In addition, a small cardiac thrombus of 1-2 mm in diameter cannot be detected on echocardiography.[3] Further precise evaluation is thus needed to clarify whether cardiac thrombus is a rare cause of cerebral infarction in DMD patients.

A hypercoagulable state is another possible cause of infarction.[15] An LVEF less than 30% in DMD patients is reportedly associated with an activated coagulation system, as indicated by elevated TAT and prothrombin fragments.[16] DMD patients with a low LVEF are thus likely in a hypercoagulable state. However, the threshold for LVEF that would trigger hypercoagulation remains unclear. In our study, 5 of 8 patients (62.5%) who underwent coagulation testing showed normal results. Among these 5 patients, LVEF values were described in 3 patients (19%, 40%, and 42%, respectively). These findings indicate that low LVEF (19% at lowest) does not always cause a hypercoagulable state.

Glucocorticoid therapy increases the risk of thrombosis.[17] However, whether patients were on steroid therapy was not described in 18 patients. We therefore do not know whether glucocorticoid therapy contributed to infarction in DMD patients. Other risk factors such as dehydration and increased blood viscosity, which may cause cerebral infarction,[3] were not identified in our 2 DMD patients with infarction. These factors were not described in other reported cases.

This study thus could not identify a single factor that could explain the cerebral infarction in DMD patients, indicating that the infarctions may be caused by multiple factors. The majority of patients with infarction had DCM with low LVEF (≤42%, median 20%). This cardiac dysfunction might represent a major risk factor. However, we could not identify cardiac thrombus in any but 2 patients with low LVEF. Recently, the concept of embolic stroke of undetermined source (ESUS) was proposed.[18] The diagnostic criteria for ESUS include: (1) nonlacunar stroke detected by CT or MRI; (2) absence of atherosclerosis causing more than equal to 50% luminal stenosis in arteries supplying the ischemic area; (3) no major-risk cardioembolic source of embolism, such as atrial fibrillation, intracardiac thrombus, or LVEF less than 30%; and (4) no other specific cause of stroke identified.[18] In our study, 5 patients showed LVEF less than 30%. These patients were, therefore, not diagnosed with ESUS. As the precise information on the brain imaging to rule out lacunar infarction was not available from most of the reported cases, we do not know how many of the rest of the patients' findings may fulfill the ESUS criteria. Further study is necessary to clarify whether infarction in some DMD patients can be categorized as ESUS.

There are no management guidelines specifically for cerebral infarction in DMD patients. Treatment for the acute-phase cerebral infarction may vary depending on the cause and situation as shown in Table 1. However, aspirin may be the choice as this is the first-line agent for the early management of patients with acute ischemic stroke.[19] For the secondary prevention of the cerebral infarction in patients with ESUS, one may assume that anticoagulants would be the choice.[18] However, 2 randomized clinical trials of anticoagulants (rivaroxaban and dabigatran, respectively) did not show significant superiority of the anticoagulants in prevention and safety compared with aspirin.[20,21] Further study is necessary for the

management and prevention (especially primary prevention) of cerebral infarction in patients with DMD.

Conclusion

Physicians should be aware of the high risk of cerebral infarction in nonambulatory DMD patients between 16 and 21 years old, particularly in those with DCM. LVEF less than around 40% might be an additional risk factor. Testing the coagulation system, echocardiography including transesophageal echocardiography to detect intracardiac thrombus, and ECG to detect fibrillation may be recommended for such high-risk patients. Further investigation is necessary to establish guideline recommendations for prevention and management of cerebral infarction in DMD patients.

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

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