Asian Biomedicine Vol. 1 No. 3 October 2007;273-278

Original article

Duchenne muscular dystrophy in northeastern Thai children: a retrospective study

Narong Auvichayapat[a], Sompon Tassniyom[a], Sarinya Srisarakham[a], Paradee Auvichayapat[b]
[a]Department of Pediatrics, [b]Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

Background: Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease. No curative treatment for DMD is known. Prednisone therapy is the first medical treatment that alters the course of DMD. Several studies about the doses and administrations of prednisone or prednisolone had been reported.
Objectives: To review clinical features, laboratory findings, and the result of treatment of DMD.
Methods: DMD patients who came to Srinagarind Hospital, Thailand from January, 1995 to January, 2007 were retrospectively analyzed.
Results: Sixty-two patients fulfilled the study criteria. All patients were male (100 %). Mean age at onset was 4.9 years. Family history was found in 10 families (16 %). The most common symptoms were weakness, standing difficulty, and gait abnormality (100, 97, and 93 % respectively). The most common clinical signs were calf hypertrophy, weakness, and Gower sign (100, 100, and 94 % respectively). Serum creatine kinase (CK) was raised in all of the patients with mean serum CK 13,026 IU/L. Fifty patients received prednisolone. Twelve received only supportive treatments. The overall outcomes of prednisolone treatment were better, same, and worse in 37, 51, and 12 % respectively. Mean age at wheel chair was 10.8 years. Three patients with associate diseases; adult respiratory distress syndrome (ARDS), Sturge Weber syndrome, and autism were presented. To the best of our knowledge, this is the first report about DMD concomitant with ARDS and DMD with Sturge-Weber syndrome. DMD with autism, a very rare occurrence, is presented.
Conclusion: Clinical features, laboratory findings, and the outcomes of treatments of 62 DMD patients were presented. Prednisolone treatment had some beneficial effects and had significant side effects. Starting with a low dose, and then increasing to high dose in the no response patient is recommended.

Keywords: Adult respiratory distress syndrome (ARDS), autism, Duchenne muscular dystrophy (DMD), prednisolone, serum CK, Sturge-Weber syndrome.

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease. Its incidence is 1:3,600 live born infant boys [1]. The essential clinical features are an X-linked recessive mode of inheritance, a distribution of weakness more proximal than distal and apparent earlier in the pelvic girdle than shoulder girdle muscles, and enlargement of calf (pseudohypertrophy) [2]. DMD follows a predictable course. The disease is remarkable for its severity with loss of walking by 13 years and death in the late teens or twenties [3]. No curative treatment for DMD is known [3]. Prednisone therapy is the first medical treatment that alters the course of DMD [4]. Several studies about the dose and administrations of prednisone or prednisolone had been reported. DeSilva (1987) reported that prednisone therapy at the dose of 2 mg/kg/day has a long-term beneficial effect in the treatment of Duchenne muscular dystrophy [4]. Brooke (1987) found improvement at the dose of 1.5 mg/kg/day [5]. Mandell (1989) reported the same benefit between prednisone at the dose of 1.5 and 0.75 mg/kg/day [6], this result was also reported by Fenichel (1991) [7]. Fenichel (1991) reported that treatment of DMD with 0.75 mg/kg/day prednisone significantly slows the progression of weakness and loss of function for at least 3 years [8]. Griggs (1993) found the benefit of prednisone in the dose of 0.75 and 0.35 mg/kg/day, but 0.75 mg/kg/day had more beneficial effect [9]. Backman (1995) reported that 0.35 mg/kg/day prednisolone can improve

Correspondence to: Dr. Narong Auvichayapat, Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; E-mail: anaron@kku.ac.th

muscle force and function in DMD [10]. In our hospital, we have used prednisolone in the various doses for 13 years. We usually start with 0.35 mg/kg/day, and then increase in the patient that has no response. The purpose of this study is to review clinical features, laboratory finding, and the result of treatment of DMD.

Materials and methods

We retrospectively reviewed the medical records of pediatric patients with DMD admitted in Srinagarind Hospital, Division of Pediatric Neurology, Khon Kaen University, which is a referral center in the northeast of Thailand, during the 13-year period from January, 1995 to January, 2007.

Inclusion criteria [1]

1. Proximal muscle weakness.
2. Calf hypertrophy.
3. Elevated serum creatinine phosphokinase level to at least ten times the upper limit of normal [11] (160 IU/L) [1].
4. Electromyography (EMG) demonstrated myopathy with or without muscle biopsy demonstrated muscular dystrophy.
5. Age less than 15 year-old.

The following data were collected: age, sex, age at onset of symptom, age at first presentation to a physician, clinical features, family history, laboratory findings and the outcome of treatment.

Reference ranges for laboratory tests

Creatine kinase (CK) <160 IU/L in children [1], 5-130 IU/L in adult [11].

Aspartate aminotransferase (AST) 1-9 years, 15-55 IU/L; 9-19 years, 5-45 IU/L [11].

Lactate dehydrogenase (LDH) 1-9 years, 150-500 IU/L; 10-19 years, 120-330 IU/L [11].

Results

General characteristics

There were 62 patients who fulfilled our study criteria. All patients were male (100 %). Ages at the first presentation to a physician were between 3.3-14.9 years, mean 8.1 years, SD 2.3 years. Their ages at onset were between 1.5-10.8 years, mean 4.9 years, SD 2.2 years. The ages at independent walking were delayed in 14 of 17 cases (76 %), mean 1.8 years, SD 0.6 years. Family history was found in 10 families (16 %) with 6 brothers, 10 uncles (mother's brother), and 1 cousin (aunt's son).

The five most common symptoms were weakness, standing difficulty, gait abnormality, frequent falling, and running difficulty (100, 97, 93, 67, and 46 % respectively). The five most common clinical signs were calf hypertrophy, weakness, Gower sign, gait abnormality, and increases lumbar lordosis (100, 100, 94, 83, and 80 % respectively). The most common motor power at presenting was grade 4 in both shoulder and hip girdle (45 % both). All of clinical features are shown in **Table 1**.

Laboratory findings

Serum CK, measured in all of the patients, was raised in all (100 %). Their serum CK were 2,302-38,407 IU/L, mean 13,026 IU/L, SD 7,925 IU/L. Serum AST, measured in 17 patients, was raised in 16 (94 %). Serum LDH, measured in 15 patients, was raised in 13 (87 %). Serum CK, measured in 34 mothers, was raised in 21 (62 %) and normal in 13 (38 %). Among 10 mothers with positive family history, there were 4 mothers that had increased serum CK but serum CK was not tested in 6 mothers. Their serum CK were 225-505 IU/L, mean 334 IU/L, SD 132 IU/L. EMG performed in 31 patients, all of them demonstrated myopathic pattern (100 %). Muscle biopsy was performed in 4 patients. All of them demonstrated muscular dystrophy (100 %). EKG with or without chest radiograph were abnormal in 3 of 7 patients. The abnormalities found in these 3 cases were biventricular hypertrophy, left ventricular hypertrophy, and sinus tachycardia (**Table 2**).

Outcomes of treatments

Fifty patients received prednisolone (81 %). Twelve patients received supportive treatments. We gave prednisolone in 3 groups; group I 0.3-0.5, group II 0.7-0.9, and group III 1-1.7 mg/kg/day in 29, 22, and 22 patients respectively. There were 25 patients who received 2 doses depended on physicians judgment. The outcomes in group I were better, same, and worse in 28, 62, and 10 % respectively. The outcomes in group II were better, same, and worse in 45, 32, and 23 % respectively. The outcomes in group III were better, same, and worse in 41, 55, and 5 % respectively. The overall outcomes were better, same, and worse in 37, 51, and 12 % respectively. In the supportive group, there were 58 % same and 42 % worse without anyone better (**Table 3**). Side effects in group I were cushingoid appearance and excessive

weight gain (13 and 29 % respectively), in group II were cushingoid, hirsutism, excessive weight gain, and abdominal pain (31, 25, 31, and 13 % respectively), and in group III were cushingoid, hirsutism, and excessive weight gain (59, 41, and 47 % respectively) (**Table 4**). The overall ages at wheel chair were between 6.8-14.7 years, mean 10.8 years, SD 2.1 years. We have followed up our patients for 80-4070 days, mean 757 days, SD 883 days.

Table 1. Clinical features in 62 patients.

Clinical features	No. (%)
Presenting symptoms	
Weakness	62/62 (100)
Standing difficulty	58/62 (97)
Gait abnormality	54/58 (93)
Frequent falling	32/48 (67)
Running difficulty	17/37 (46)
Climbing stair difficulty	11/39 (28)
Leg pain/calf pain	8/35 (23)
Loss of ambulation	4/62 (6)
Rigid calves	2/32 (6)
Frequent choking	1/62 (2)
Physical examination	
Calf hypertrophy	62/62 (100)
Gower sign	
- Positive	58/62 (94)
- Cannot stand	4/62 (6)
Gait abnormality	
- Spastic gait (contracture of Archilles tendons)	45/54 (83)
- Waddling gait	9/54 (17)
Increased lumbar lordosis	43/54 (80)
Motor power at presenting	
- Shoulder girdle	
Grade 3/5	9/62 (15)
Grade 4/5	28/62 (45)
Grade 5/5	25/62 (40)
- Pelvic girdle	
Grade 1/5	1/62 (2)
Grade 2/5	7/62 (11)
Grade 3/5	26/62 (42)
Grade 4/5	28/62 (45)

Table 2. Laboratory findings in 62 patients.

Laboratory findings	No. (%)	Range (mean SD)
Increased CK	62/62 (100)	2,302-38,407; 13,026 7,925 IU/L
Increased AST	16/17 (94)	22-540; 256 140 IU/L
Increased LDH	13/15 (87)	267-2,846; 1,438 1,006 IU/L
Increased CK in the mother	21/34 (62)	20-2,222; 256 378 IU/L
EMG: myopathic type	31/31 (100)	-
Muscle biopsy: muscular dystrophy	4/4 (100)	-
Abnormal EKG/chest radiograph	3/7 (43)	-
Biventricular hypertrophy	1/7 (14)	-
Left ventricular hypertrophy	1/7 (14)	-
Sinus tachycardia	1/7 (14)	-

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Table 3. Outcomes of treatment in 60 cases*.

Treatment	No. of Patients (%)	Outcomes; No. (%)		
		Better	Same	Worse
Prednisolone	50* (81)			
Group I, 0.3-0.5 mg/kg/day	29	8 (28)	18 (62)	3 (10)
Group II, 0.7-0.9 mg/kg/day	22	10 (45)	7 (32)	5 (23)
Group III, 1-1.7 mg/kg/day	22	9 (41)	12 (55)	1 (5)
Total	73**	27 (37)	37 (51)	9 (12)
Supportive treatments	12 (19)	-	7 (58)	5 (42)

*Two patients with prednisolone were lost to follow-up. **Twenty-five patients received 2 doses of prednisolone.

Table 4. Side effects in 48 patients received prednisolone.

Treatment	No. of Patients (%)	Cushingoid No. (%)	Hirsutism No. (%)	Excessive weight gain* No. (%)	Abdominal pain No. (%)
Prednisolone					
0.3-0.5 mg/kg/day	15	2 (13)	0 (0)	3 (20)	0 (0)
0.7-0.9 mg/kg/day	16	5 (31)	4 (25)	5 (31)	2 (13)
1-1.7 mg/kg/day	17	10 (59)	7 (41)	8 (47)	0 (0)
Total	48	17 (35)	11 (23)	16 (33)	2 (4)

* Body weight raised more than 2 SD of age.

Associate diseases

There were 3 patients who had associate diseases; adult respiratory distress syndrome (ARDS), Sturge Weber syndrome, and autism.

Patient 1. A 6 year-old boy presented with standing difficulty since age 4 years. He had calf hypertrophy and positive Gower sign. The motor power of pelvic girdle was grade 3, and shoulder girdle was grade 5. His serum CK and LDH were 16,514 and 1509 IU/L respectively. The EMG revealed myopathic pattern. He had never received corticosteroids. He had loss of ambulation since 7 year-old. When he was 10 year-old, he came to our hospital with fever, cough, and dyspnea for 12 hours. The chest radiograph revealed characteristic diffuse alveolar-interstitial infiltrates in all lung fields (**Fig. 1**). Complete blood count revealed leukocytosis with shifting to the left. Arterial blood gas with 100 % oxygen, PO_2 29.9 mmHg, PCO_2 30.8 mmHg. He was admitted to the pediatric intensive care unit. After received ceftazidime and cloxacillin with ventilator support, he improved and was discharged. Tracheal suction culture, blood culture, mycoplasma titer, and mellioidosis titers were negative. EKG revealed biventricular hypertrophy. Echocardiographic examination revealed good ventricular function with 61.2 % ejection fraction. We had followed him until 12 year-old and he was still well except for loss of ambulation.

Patient 2. A 7 year-old boy presented with weakness of legs, difficulty in climbing stairs, frequent falling, and leg pain for 2 months. He never had seizure. Port-wine stain hemangioma was found on his left cranial nerve V_1 and V_2 distribution since he was born. Sturge-Weber syndrome was diagnosed. He had atrophy of his gluteal area, calf hypertrophy

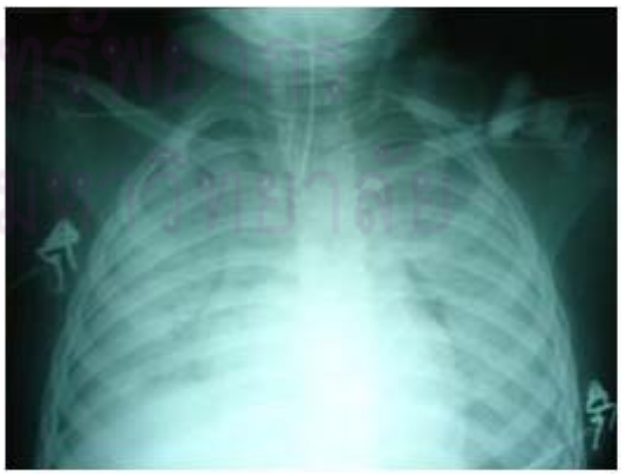

Fig. 1 The chest radiograph reveals characteristic diffuse alveolar-interstitial infiltrates in all lung fields.

and positive Gower sign. His serum CK was 29,000 IU/L and serum CK of his mother was 219 IU/L. We gave him prednisolone 0.3 mg/kg/day with improvement of motor power and stable until he is now 11 year-old.

Patient 3. A 28 month-old boy came to our hospital with the problems of delayed speech, nonverbal communication, no social playing, and very narrow interests. He met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for autism spectrum disorders. He developed weakness of both legs and standing difficulty since he was 4 year-old. Physical examination revealed calf hypertrophy and positive Gower sign. His serum CK was 6,053 IU/L. EKG revealed sinus tachycardia with nonspecific ST-T change. Chest radiograph was normal. We gave him prednisolone at 0.3 mg/kg/day and he had slightly improved. Now he is 8 year-old, his motor power is worse. He cannot stand and is easily fatigued.

Discussion

We retrospectively reviewed 62 patients in northeastern Thailand. The mean age at onset of symptoms was 4.9 years but the mean age at first presentation to a physician was 8.1 years. This indicates that DMD has an insidious onset and is a slow progressive disease. Indeed, the age at onset may be earlier than this because the age at independent walking was delayed (mean 1.8 year). We found the delay of independent walking in 76% which was higher than the study in Estonia that found in only 36 % [12]. Smith SA stated that the clinical manifestations are typically not recognized until 3 years of age or later [13]. But we think the clinical manifestations may be earlier if the parents pay more attention. All of our patients were male. There were 10 families (16 %) that had a history of DMD; all of them were in the mothers families. These findings indicate the exclusive X-linked recessive inheritance of DMD. The clinical features of our patients were typical as reported in other studies [1, 2, 12, 13].

Serum CK was greatly elevated in all of our patients as in other studies [1, 13]. Other muscle enzymes, serum AST and LDH were also elevated but were not as high as serum CK. In our area, there were insufficient diagnostic tools such as EMG, muscle biopsy, and DNA analysis. So serum CK is the important diagnostic tool. Serum CK in the mother was slightly to moderately increased in 62 % and was increased in all of the positive family history mothers. Therefore serum CK should be evaluated in all of the mothers who have DMD children for the benefit of genetic counseling. We performed cardiac evaluation in a few cases and found 43 % with abnormalities. So, cardiac evaluation should be done.

In our institute, most of the patients received prednisolone. We usually begin with low dose 0.3-0.5 mg/kg/day for reduction of its side effects. We will increase to moderate or high dose in the patient who does not response to low dose. We found that 28 % were better with low dose and the side effects were less, only 13 % had cushingoid appearance and 20 % had excessive weight gain. When we gave the higher dose, 41-45 % were better but the side effects were much more. There was no patient who improved in the supportive group. In our opinion, prednisolone should be tried with the minimal dose and increased after there is no response.

There were 3 patients who had associate diseases; ARDS, Sturge-Weber syndrome, and autism. To the best of our knowledge, there is no previous report of co-occurrences between ARDS, Sturge Weber syndrome and DMD. There were few reports about the association between autism and DMD [14-17]. ARDS in DMD may be due to 3 factors; impaired cardiac function, impaired pulmonary function, and infection. Although his EKG revealed biventricular hypertrophy, the echocardiographic examination revealed good ventricular function, so his cardiac function may be good or slightly impaired. We think that the pre-existent impairment of pulmonary function in DMD triggered by infection with or without the impairment of cardiac function may be the cause of ARDS in this case. We cannot explain the relation between DMD and Sturge-Weber syndrome. This may be only an accidental co-occurrence. Further observation is needed. There were only 19 children who had DMD with autism previously reported. Komoto (1984) was the first who reported a boy with autism and DMD [14]. Kumagai (2001) reported 8 DMD and 2 Becker muscular dystrophy patients with autism [15]. Zwaigenbaum (2003) reported 2 cases. Wu (2005) found 8 patients diagnosed as autism in 159 DMD patients (5 %) [17]. Dystrophin is a protein that is most abundant in muscle. Dystrophin is also found in the brain at approximately 10 % of the level found in skeletal muscle [17]. Cognitive impairments in DMD likely occur as the result of expression of the dystrophin gene in the

central nervous system. Verbal deficits are particularly prominent in boys with DMD [18]. Kaplan (1986) reported 3 patients with expressive language and ultimately found these have muscular dystrophy [19]. Appleton (1991) reported that DMD, like autism, had a greater head circumference than a normal population and were found to be significantly intellectually impaired, particularly in verbal and language skills [20]. Taken together, we think DMD and autism have some association and share some part of the same pathogenesis involving dystrophin. This needs further study of the association between these two diseases.

The author has no conflict of interest to declare.

References

1. Sarnat HB. Duchenne and Becker muscular dystrophy. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders. 2004; p. 2060-4.
2. Brett EM, Lake BD. Neuromuscular disorders: I. Primary muscle disease and anterior horn cell disorders. In: Brett EM, ed. Paediatric neurology. 3rd ed. New York:Churchill Livingstone;1997. p. 57-66.
3. Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2004;(2):CD003725. Review.
4. DeSilva S, Drachman DB, Mellits D, Kuncl RW. Prednisone treatment in Duchenne muscular dystrophy, long-term benefit. Arch Neurol. 1987;44: 818-22.
5. Brooke MH, Fenichel GM, Griggs RC, Mendell JR, Moxley RT 3rd, Miller JP, et al. Clinical investigation of Duchenne muscular dystrophy. Interesting results in a trial of prednisone. Arch Neurol. 1987;44:812-7.
6. Mendell JR, Moxley RT, Griggs RC, Brooke MH, Fenichel GM, Miller JP, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med. 1989;320:1592-7.
7. Fenichel GM, Mendell JR, Moxley RT 3rd, Griggs RC, Brooke MH, Miller JP, et al. A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. Arch Neurol. 1991; 48:575-9.
8. Fenichel GM, Florence JM, Pestronk A, Mendell JR, Moxley RT 3rd, Griggs RC, et al. Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. Neurology. 1991;41:1874-7.
9. Griggs RC, Moxley RT 3rd, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Duchenne dystrophy: randomized, controlled trial of prednisone (18 months) and azathioprine (12 months). Neurology. 1993;43: 520-7.
10. Backman E, Henriksson KG. Low-dose prednisolone treatment in Duchenne and Becker muscular dystrophy. Neuromuscul Disord. 1995;5:233-41.
11. Nicholson JF, Pesce MA. Laboratory medicine and reference tables. In: Behrman RE, Kliegman RM, Arvin AM, eds. Nelson textbook of pediatrics. 15th ed. Philadelphia:Saunders; 1996; p. 2031-58.
12. Talkop UA, Klaassen T, Piirsoo A, Sander V, Napa A, Essenson E, et al. Duchenne and Becker muscular dystrophies: an Estonian experience. Brain Dev. 1999; 21:244-7.
13. Smith SA, Swaiman KF. Muscular dystrophies. In: Swaiman KF, Ashwal S, eds. Pediatric neurology: principle and practice. 3rd ed. St. Louis:Mosby. 1999; p. 1235-43.
14. Komoto J, Usui S, Otsuki S, Terao A. Infantile autism and Duchenne muscular dystrophy. J Autism Dev Disord. 1984;14:191-5.
15. Kumagai T, Miura K, Ohki T, Matsumoto A, Miyazaki S, Nakamura M. Central nervous system involvements in Duchenne/Becker muscular dystrophy (in Japanese). No-to-Hattatsu 2001;33:480-6.
16. Zwaigenbaum L, Tarnopolsky M. Two children with muscular dystrophies ascertained due to referral for diagnosis of autism. J Autism Dev Disord. 2003;33: 193-9.
17. Wu JY, Kuban KC, Allred E, Shapiro F, Darras BT. Association of Duchenne muscular dystrophy with autism spectrum disorder. J Child Neurol. 2005;20: 790-5.
18. Dorman C, Hurley AD, D'Avignon J. Language and learning disorders of older boys with Duchenne muscular dystrophy. Dev Med Child Neurol. 1988;30: 316-27.
19. Kaplan LC, Osborne P, Elias E. The diagnosis of muscular dystrophy in patients referred for language delay. J Child Psychol Psychiatry. 1986;27:545-9.
20. Appleton RE, Bushby K, Gardner-Medwin D, Welch J, Kelly PJ. Head circumference and intellectual performance of patients with Duchenne muscular dystrophy. Dev Med Child Neurol. 1991;33:884-90.