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Original Article

Evaluation of the relationship between urogenital abnormalities and neuromuscular disorders

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Abstract. Because of its striated muscle origin; the cremaster muscle may possibly be affected by neuromuscular diseases and may cause the increased incidence of undescended testes and other urogenital malformations. Therefore we aim at determining the frequency of inguinopenoscrotal abnormalities in children with muscle disease.This study was conducted at the Izmir Dr.Behcet Uz Children's Hospital from May 2004 through April 2009. Twenty eight normal muscle and 105 boys holding diagnoses of neuromuscular disorders which were confirmed by muscle biopsy were included in this study. Detailed clinical information, physical and laboratory examination findings were obtained from patient files. All findings were evaluated statistically. The mean age of all boys was 6.42 (± 3.89), years. Dystrophies were diagnosed in 79 (75.2%) patients. Other disorders were 5 primary, 7 inflammatory and 7 metabolic/mitochondrial myopathies and 7 neuropathies. Twenty seven (25.7%) patients had similarly affected family members. Consanguinity rate was 24.7%. Alterations in serum enzymes, EMG pathologies and fiber type disproportions were determined in 88 (83.8), 82 (78%) and 28 (26.6%) of the patients respectively. Urogenital malformations were detected in 11 (8.27%) boys. Although both in Spearman's Correlation Analysis and in Fisher exact Chi-Square test, there were no statistical significances between the types of neuromuscular disease and urogenital malformations (p=0.344 and p=0.457), the odds ratio for urogenital pathologies was found 2.83. This result supported that urogenital abnormalities were more common in children with neuromuscular disorders than control cases.Congenital muscle disease may create a disturbance during development of inguinal region possibly with influence of cremaster muscle or other inguinal tissues. Therefore children with muscle diseases must be more carefully physically examined for the presence of urogenital pathologies and paradoxically children with urogenital pathologies must be neurologically examined for the presence of any neuromuscular disorders.

Key words: Cremaster muscle, neuromuscular disorders, childhood, undescended testes

1. Introduction

Undescended testes is a relatively common congenital malformation, occurring in up to one third of premature male newborns and 3 to 5 percent of term male infants (1-5). By three months of age the incidence reduces to 0.8 percent and does not change until adulthood (1). The indirect inguinal hernia originates from the failure of embryonic closure of processus vaginalis after the testicle passes through the inguinal canal. In the communicating (congenital) hydrocele, a patent processus vaginalis permits flow of peritoneal fluid into the scrotum. Indirect inguinal hernias are associated with this type of hydrocele. The mechanisms involved in testicular descent and urogenital development still remain unknown, but are probably heterogeneous (3). In-utero endocrine disruption, the structural alterations of regional tissues and deficiency in sympathetic innervations are most claimed etiologic factors (1-5).

The cremaster muscle (CM) has its origin in the gubernaculum and it is believed to develop through transdifferentiation of the smooth muscle (6-9). Although it is a striated muscle, it has no

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Table 1 The detailed clinical characteristics of the patients

Disease (patients n:133)	Mean age	Presence of undescended testes	Presence of urogenitale or penoscrotal pathology	CPK level	Transaminase level	Presence of sarkolemmal staining defect	Myofiber type disproportion	Presence of pathological EMG findings	Consanguinity	Positive family history
n=28 Nonspecific/ minimal changes	6.7± 4.95	n= 0 (0 %)	n= 1 (3.7 %)	Normal or mild↑ n= 21 (75 %) high n= 8 (25 %)	Normal or mild↑ n= 22 (78.6 %) high n= 6 (21.4 %)	n= 0 (0 %)	n= 6 (21.4 %)	n= 11* (39.3 %) * EMG was not performed in 5 cases	n= 3 (10.7 %)	n= 2 (7.1 %)
n= 5 Primary Myopathy	5.6± 3.3	n= 2 (40%)	n= 2 (40%)	Normal or mild↑ n= 3 (60 %) high n= 2 (40 %)	Normal or mild↑ n= 3 (60 %) high n= 2 (40 %)	n= 0 (0%)	n= 3 (60%)	n= 5 (100%)	n= 1 (20%)	n= 2 (40%)
n= 14 Dystrophin (+) Muscular Dystrophy	8.1± 4.8	n= 0 (0 %)	n= 0 (0 %)	Normal or mild↑ n= 1 (7.1 %) high n= 13 (92.8 %)	Normal or mild↑ n= 7 (50 %) high n= 7 50 %)	n= 7 (50 %)	n= 8 (57.1 %)	n= 12* (85.7 %) * EMG was not performed in 1 case	n= 2 (14.2 %)	n= 4 (28.4 %)
n= 65 Dystrophin (-) Muscular Dystrophy	6.8± 3.1	n= 1 (1.5 %)	n= 5 (7.8 %)	Normal or mild↑ n= 0 (0 %) high n= 65 (100 %)	Normal or mild↑ n= 8 (12.7 %) high n= 57 (87.6 %)	n= 65 (100 %)	n= 10 (15.4 %)	n= 54* (83.1 %) * EMG was not performed in 1 case	n= 13 (20 %)	n= 18 (27.7 %)
n= 7 Metabolic and mitochondrial myopathy	10.6± 4.5	n= 1 (14.3 %)	n= 1 (14.3 %)	Normal or mild↑ n=4 (57.2%) high n= 3 (42.8%)	Normal or mild↑ n=4 (57.2%) high n= 3 (42.8%)	n= 0 (0 %)	n= 3 (42.8 %)	n= 4 (57.2 %)	n= 6 (85.7%)	n= 1 (14.3 %)
n= 7 Neuropathy	1.7± 3.3	n= 0 (0 %)	n=2 (28.6 %)	Normal or mild↑ n= 5 (71.4%) high n= 2 (28.6%)	Normal or mild↑ n= 5 (71.4%) high n= 2 (28.6%)	n=1 (14.3 %)	n= 4 (57.2 %)	n= 3* (42.8 %) * EMG was not performed in 1 case	n= 3 (42.8 %)	n= 2 (28.6 %)
n= 7 Inflammatory myopathy	7.3± 4.07	n= 0 (0 %)	n=0 (0 %)	Normal or mild↑ n=4 (57.2%) high n= 3 (42.8%)	Normal or mild↑ n=4 (57.2%) high n= 3 (42.8%)	n= 0 (0 %)	n= 0 (0 %)	n=4 * (55.2 %) * EMG was not performed in 1 case	n= 1 (14.2 %)	n= 0 (0 %)
P	0.390	0.888	0.344	0.093	0.173	0.000	0.450	0.898	0.006	0.563

voluntary control (9). It is also suggested that the involuntary contractions of cremaster muscle mediated by hormonal and neurological effects play a major role in the active step in testicular descent (7,8). Therefore it plays an indispensable role in the descent of testis as well as in the other inguinoscrotal pathologies (9,10).

Hypospadias are among the most common birth defects of the male genitalia that presents an abnormally placed urethral meatus (opening) (5). Widely varying incidences have been reported from 0.02% to 0.8% (3-5,11). Prenatal testosterone promotes migration of skin fibroblasts to fully enclose the penile urethra in fetal males (11). Similarly, other urogenital abnormalities, failure of adequate prenatal androgen effect or various factors interfering with androgen effect are thought to be involved in the etiopathogenesis of hypospadias (5,11).

Due to its striated muscle origin; the cremaster muscle may possibly be affected by neuromuscular diseases and may cause the increased incidence of undescended testes and other inguinopenoscrotal abnormalities. In the present study we aimed to retrospectively reviewing the records of 133 boys who held diagnoses of different neuromuscular diseases and determining the frequency of urogenital malformations in these children.

2. Materials and methods

The study was performed at Izmir Dr.Behcet Uz Children's Hospital from May 2004 through April 2009. A hundred and thirty threee boys with neuromuscular disorders were included in this study. A hundred and five of whom presented muscle pathologies which were confirmed by muscle biopsy. Other 28 muscle samples were evaluated as normal. The samples were obtained from gastrocnemius muscle except in a patient with Kearns Sayre disease. The sample in this boy was obtained from deltoid muscle. Samples were frozen in isopentane cooled in liquid nitrogen and 6 to 16 micron sections were cut using cryostat. Slides were stained with routine hematoxylin eosin, histochemically with Gomori's trichrome, modified Gomori's trichrome (Engel-Cunningham modification), oil red-O, PAS, D-PAS stains; enzyme histochemically with nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH) and cytochrome oxidase (COX) stains. Sarcolemmal spectrin (Novo-castra, UK, NCL-spec1) dystrophin N-terminus (Novo-castra, UK, NCL-dys3), adhalin (Novo-castra, UK, NCL-a-sarc), beta, delta and gamma sarcoglicans (Novo-castra, NCL-b- sarc, NCL-d-sarc, NCL-g-sarc), dysferlin (Novo-castra, NCL-hamlet2), laminin alpha-2 chain (Novo-castra, UK, NCL-merosin) and perinuclear emerin (Novo-castra, UK, NCL-emerin) stainings were also performed, immunohistochemically. Myosin heavy chain fast (Novo-castra, UK, NCL-MHCf) antibody was used for discriminating of fiber type. Individual patient database was reviewed in all cases and detailed clinical information of patients was recorded including age, status of functional ability associated complaints such as muscle weakness and respiratory distress, detailed perinatal history, family history and consanguinity. Neurological examination and laboratory findings were also evaluated.

Spearman's Correlation analysis and Fisher exact Chi Square test for the comparison between groups were performed for statistical analysis. P values less than 0.05 were considered to be statistically significant. Odds ratios were also calculated for evaluating the incidences of undescended testes and other inguinopenoscrotal abnormalities in the children with neuromuscular disorders. Values greater than 1 were considered to have statistical significance.

3. Results

The mean age of the patients at the time of biopsy was 6.42 years (± 3.89), ranging from 4 months to 17 years. The detailed clinical characteristics of the boys are presented in Table 1. The majority of patients presented some degree of muscle weakness. Others were suspected to have a neuromuscular disorder with high creatine kinase (CK) and/or transaminase levels. In 7 floppy infants, muscle biopsy was performed for differential diagnosis. Twenty seven (25.7%) patients had similarly affected family members. Consanguinity rate was 24.7% (n= 26). Physical examination at the time of diagnosis revealed muscle weakness in all patients. Eighty eight patients (66.16%) presented at least one of the muscle serum enzymes altered. Needle electromyogram was performed in only 101 patients (96.1 %) and was interpreted as myopathic in 77 (73.3%), neuropathic in 5 (4.7%) and normal in 19 (18.09%). Final diagnosis was assigned on the basis of muscle biopsy findings (Fig. 1). In 28 boys (21.05 %), nonspecific myopathic changes such as alterations of myofiber size and shape, increased number of internal nuclei, fiber degeneration, and fiber type disproportion were determined and they were also classified as normal muscle with nonspecific

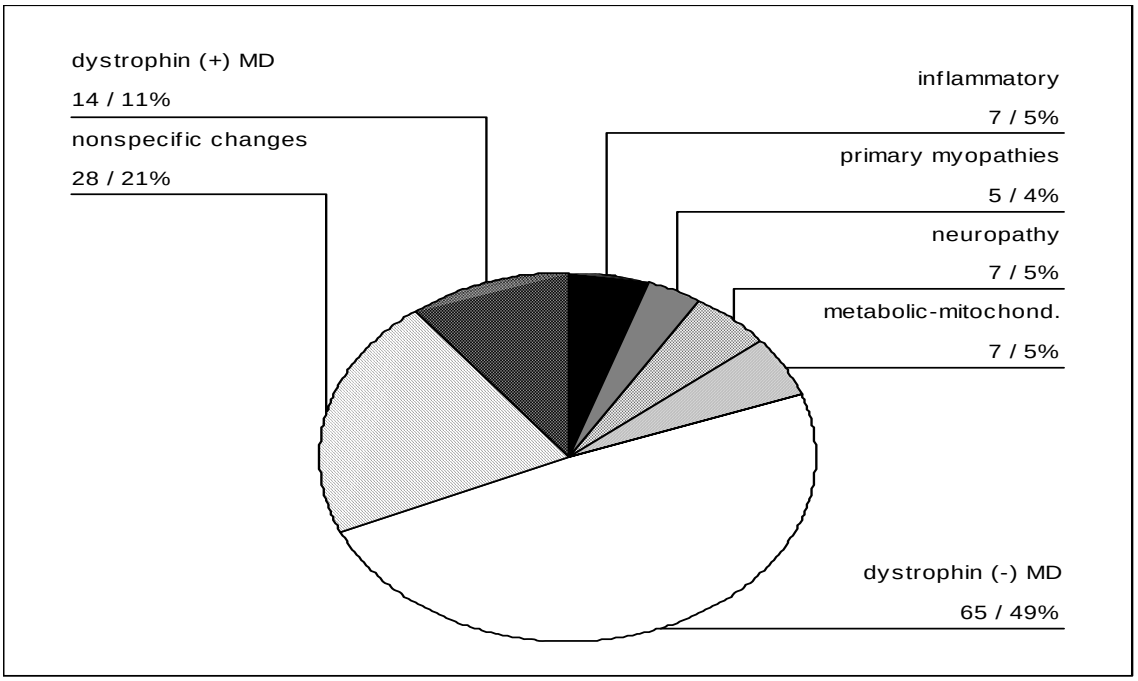

Fig. 1. Distribution of the cases according to histopathological diagnosis (n= 133).

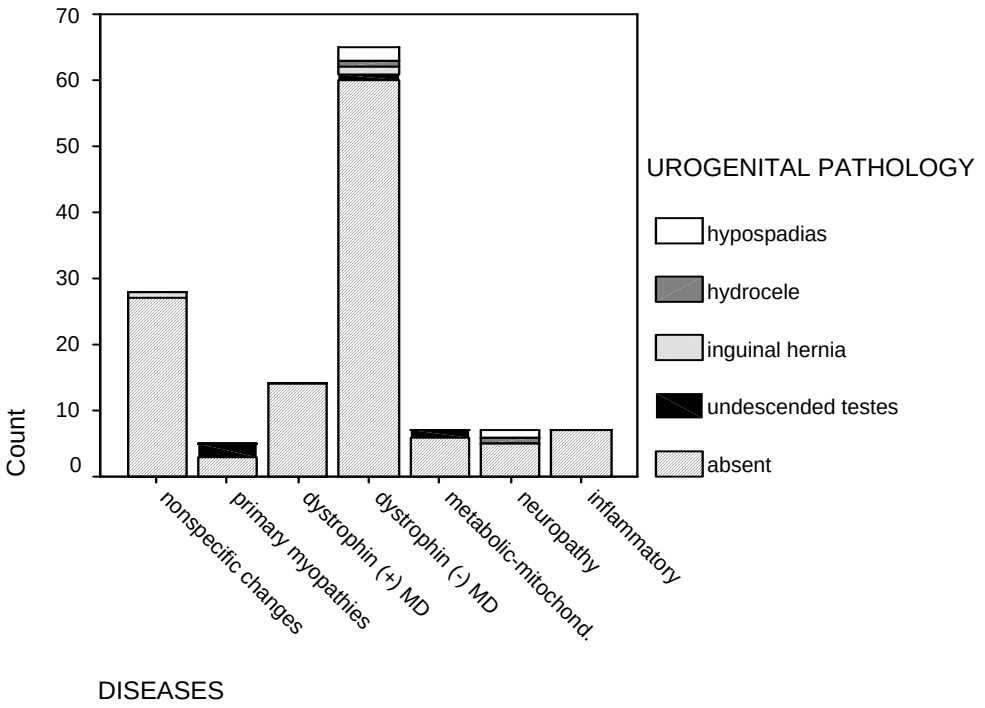

Fig. 2. Distribution of the inguinopenoscrotal abnormalities of patients according to the neuromuscular disorders.

minimal changes. Myofibrillar myopathy (MFM) and centronuclear myopathy (CNM) were also diagnosed with muscle biopsy and were included in the primary myopathy group. In 3 patients with McArdle disease, carnitine deficiency myopathy and Kearns Sayre disease, the diagnoses were confirmed with electron microscopic and/ or genetic investigations. They were classified as metabolic and mitochondrial diseases. Type 1 fiber atrophy was determined in 4 patients (3.8 %), while type 2 fiber atrophy in 24 (22.8 %). In the other 77 patients (73.3%) fiber type distributions was normal. Muscular dystrophies (MD) were the most common disease (75.2%) in this series and in 14 patients with muscular dystrophy, sarcolemmal dystrophin was present. In 7 of these patients (50%), merosin (n=1), dysferlin (n=1) and sarcoglicans (n=5) defects were determined. The presence of neuromuscular disorders was suspected in 7 patients with muscular dystrophy (6.6%) because of high transaminase levels. In 4 of these patients (3.8%), high transaminase levels were determined during preoperative examination for inguinopenoscrotal reconstructive surgery of undescended testes, hydrocele, inguinal hernia or hypospadias.

Urogenital malformations were determined in 10 (9.5%) patients and in 1 (3.5%) normal cases. These abnormalities consisted of 4 undescended testes, 2 congenital communicating hydrocele, 2 indirect inguinal hernia and 3 hypospadias. The determined urogenital abnormalities according to the various etiologies are summarized in (Fig. 2). In Spearman's Correlation Analysis, there were statistical significances between the types of neuromuscular disease and the presence of consanguinity (p= 0.006) and presence of sarcolemmal staining defects (p= 0.000). In Fisher exact Chi Square test, no statistical significance between neuromuscular disorders and inguinopenoscrotal abnormalities was found (p= 0.457). As well as, the odds ratios for urogenital pathologies were computed and they was found 2.83.

4. Discussion

The estimated incidence of various inguinopenoscrotal abnormalities in population is <3% (1-5,9). In a recent study from Iran, the highest prevalence in the literature of these malformations was reported as 5.17% (4). The authors claimed that it was associated with the geographic and racial differences. They also suggested that adequate public education and medical care are needed to improve the outcome and necessary to avoid later complications (4). Yucesan et al (3) found these rates as 0.9 % for undescended testes and as 1.4 % for inguinal hernia among the Turkish school children. In our study, we have presumed the normal percentages as 0.8 % for undescended testes and as 2.7 % for inguinoscrotal abnormalities and hypospadias according to the literature (1-5, 9). In control cases, we found only one urogenital abnormality. The odds ratio for urogenital pathologies was found 2.83. These results supported that urogenital abnormalities were more common in children with neuromuscular disorders than normal population. On the contrary, no statistical significance between neuromuscular disorders and urogenital malformation was found in Chi Square test (p= 0.457). We have thought that this absence of statistical significance may be associated with the number of patients of this series. Therefore, the incidence of urogenital abnormalities must be examined in larger series of neuromuscular disorders.

As most authors have accepted that the inguinopenoscrotal abnormalities were isolated congenital malformations caused by the various disturbing effects on the tissues of this region (6-8, 10), reports evaluating the etiopathogenesis of undescended testes and other inguinoscrotal pathologies have usually dealt with the alterations of tissues associating the processus vaginalis and gubernaculums (6-10). Many detailed examinations of cremaster muscles aimed at enlightening the etiology of inguinoscrotal pathologies also have been performed. However, the alterations in cremaster muscle or other striated muscles in children with neuromuscular disorders have not previously been comparatively evaluated according to the presence of either undescended testes or urogenital pathologies (5-13). In the present study, we determined two undescended testes among patients with primary myopathies. One of these patients has centronuclear myopathy and other has myofibrillar myopathy (12-16). Both diseases may possibly create the severe cremasteric dysfunction in utero (14-16). On the other hand, no urogenital pathologies were determined in the patients with acquired or early adulthood presented muscle diseases such as inflammatory myopathy, Kearns Sayre disease, McArdle disease and carnitine deficiency disease (2,13, 17).

Similarly not only undescended testes but also other urogenital malformations were found in patients with congenital neuromuscular disorders. Among these patients, the lowest incidence of urogenital malformations was found in patients with MD (7.8%), especially sarcolemmal

dystrophin positive MD (0%). It is known that the MDs rarely become manifest in utero or in neonatal period because defective proteins are necessary to promote membrane stability, particularly during muscle contractions (18-20). The degree of muscle injuries in the patients with MD gradually increases in postpartum period (18-20). Therefore we have thought that MD doesn't provoke the development of urogenital malformations. Finally all previous studies have evaluated the etiopathogenesis of urogenital malformations by inductive manner and it was accepted that all inguinopenoscrotal abnormalities were localized malformations caused by focal adverse effects of hormonal, neurological or other deficits (5-10). In the present study, we have evaluated the etiopathogenesis of urogenital malformations and especially undescended testes by deductive manner. We found that the undescended testes and inguinopenoscrotal abnormalities are more common in children with neuromuscular disorders than in the normal population (1-10).

In conclusion, although performed in a limited number of patients, this study shows that all muscle diseases may create a disturbance of testicular descend possibly with influence of cremaster muscle or other inguinal tissues. Therefore children with muscle diseases must be more carefully physically examined for presence of urogenital pathologies and paradoxically children with urogenital pathologies must be neurologically examined for the presence of neuromuscular disorders.

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