Arq Neuropsiquiatr 2005;63(3-B):785-790

ULLRICH CONGENITAL MUSCULAR DYSTROPHY AND BETHLEM MYOPATHY

Clinical and genetic heterogeneity

Umbertina Conti Reed[1], Lucio Gobbo Ferreira[2], Enna Cristina Liu[3], Maria Bernadete Dutra Resende[2], Mary Souza Carvalho[2], Suely Kazue Marie[1], Milberto Scaff[4]

ABSTRACT - Ullrich congenital muscular dystrophy (UCMD), due to mutations in the collagen VI genes, is an autosomal recessive form of CMD, commonly associated with distal joints hyperlaxity and severe course. A mild or moderate involvement can be occasionally observed. *Objective:* To evaluate the clinical picture of CMD patients with Ullrich phenotype who presented decreased or absent collagen VI immunoreactivity on muscular biopsy. *Results:* Among 60 patients with CMD, two had no expression of collagen V and their clinical involvement was essentially different: the first (3 years of follow-up) has mild motor difficulty ; the second (8 years of follow-up) never acquired walking and depends on ventilatory support. A molecular study, performed by Pan et al. at the Thomas Jefferson University, demonstrated in the first a known mutation of Bethlem myopathy in COL6A1 and in the second the first dominantly acting mutation in UCMD and the first in COL6A1, previously associated only to Bethlem myopathy, with benign course and dominant inheritance. *Conclusion:* Bethlem myopathy should be considered in the differential diagnosis of UCMD, even in patients without fingers contractures; overlap between Ullrich and Bethlem phenotypes can be supposed.

KEY WORDS: Ullrich congenital muscular dystrophy, congenital muscular dystrophy, joint hyperlaxity, collagen VI, Bethlem myopathy.

Distrofia muscular congênita com hiperextensibilidade articular distal (Ullrich) e miopatia de Bethlem: heterogeneidade clínica e genética

RESUMO - A distrofia muscular congênita (DMC) com hiperextensibilidade articular distal (fenótipo Ullrich) associa-se a mutações nos genes do colágeno VI e corresponde a um grave quadro congênito de herança autossômica recessiva e curso progressivo, ocasionalmente mostrando menor gravidade. *Objetivo:* Avaliar o quadro clínico dos pacientes com DMC tipo Ullrich que apresentam imunoexpressão baixa ou ausente do colágeno VI na biópsia muscular. *Resultados:* Entre 60 pacientes com DMC, dois mostravam imunomarcação negativa do colágeno VI. Mostravam-se clinicamente essencialmente diferentes: o primeiro, com 8 anos de idade e três de seguimento mostra leve dificuldade motora; o segundo, com 14 anos de idade e 8 de seguimento, não deambula e apresenta insuficiência respiratória. O estudo molecular, realizado na Thomas Jefferson University por Pan et al., revelou no primeiro, no gene COL6A1, mutação típica da miopatia de Bethlem, que tem curso benigno e herança autossômica dominante; e no segundo a primeira mutação de efeito dominante e do gene COL6A1, previamente associado apenas à miopatia de Bethlem. *Conclusão:* A miopatia de Bethlem deve constar no diagnóstico diferencial da DMC tipo Ullrich, mesmo na ausência das típicas contraturas dos dedos; pode existir sobreposição dos fenótipos Ullrich e Bethlem.

PALAVRAS-CHAVE: distrofia muscular congênita; hiperextensibilidade articular, colágeno VI, fenótipo Ullrich, miopatia de Bethlem.

Bethlem myopathy is a dominantly inherited disorder caused by mutations in the three genes of collagen VI, i.e. COL6A1 (21 q22.3), COL6A2 (21 q22. 3) and COL6A3 (2 q37)[1-4]. Although Bethlem myopathy is clinically heterogeneous, most of patients have benign course. The onset may be in the neonatal

Departamento de Neurologia da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil (FMUSP): [1]Professor Associado; [2]Doutor; [3]Acadêmica da FMUSP; [4]Professor Titular.

Received 5 January 2005, received in final form 8 April 2005. Accepted 21 May 2005.

Dra. Umbertina Conti Reed - Departamento de Neurologia, Hospital das Clínicas FMUSP - Av. Enéas de Carvalho Aguiar 255/5º andar, sala 5131 - 05403-900 São Paulo SP - Brasil. E-mail: ucontireed@hcnet.usp.br

period, childhood or adolescence and contractures of fingers, elbows and ankles joints represent a hallmark of this phenotype[3-5]. In addition, from 2001, the deficiency of collagen VI in muscle has been associated with Ullrich scleroatonic congenital muscular dystrophy (UCMD) that is caused by different types of recessive and dominantly acting mutations in the same three collagen VI genes[4,6-8]. UCMD is clinically less heterogeneous than Bethlem myopathy; however, although the majority of patients have the classic severe form that is characterized by neonatal muscle weakness, proximal joint contractures, hyperlaxity of the distal joints and severe course[4], milder patients have now been reported[9].

Both, Ullrich and Bethlem phenotypes are linked to the COL6A1, COL6A2 or COL6A3 genes, encoding respectively the alpha 1, alpha 2 and alpha 3 chains of collagen VI, and show clinical and genetic heterogeneity; therefore mutation detection in essential in these disorders for allowing the correct diagnosis, the establishment of prognosis and an accurate genetic counseling.

For emphasizing this clinical and genetic heterogeneity, we report on two patients with distal joint hiperlaxity, the first with a mild to moderate myopathic phenotype including joint hyperlaxity and the second with a severe Ullrich phenotype. In both, a molecular analysis was performed at the Thomas Jefferson University, Philadelphia, by Pan et al.[7] and revealed in the first a dominantly acting mutation in the COL6A1 gene, that has not been described yet, and in the second a heterozygous in-frame deletion in the COL6A1 that has been previously described in Bethlem myopathy[10-11].

METHOD

Sixty children with clinical and histopathological diagnosis of congenital muscular dystrophy (CMD) had their muscle samples evaluated immunohistochemically by means of immunofluorescency or immunoperoxidase methods, utilizing antibodies for dystrophin (C-terminal), merosin (80 Kda and 300 Kda), sarcoglycans (γ, γ, y and γ-SGs) and dystroglicans (γ-DG and γ-DG)[12]. Among them, 7 presented marked distal hyperlaxity and had their muscle samples also tested for collagen VI immunoreactivity using Hybridoma Bank antibody, code 5C6,1/100. In two patients (Cases 1 and 2) collagen VI immunoreactivity was absent.

CASES

Case 1 – A 4 year-9 month-old male was born at term following an uneventful pregnancy from non consanguineous parents who had already two healthy children. At birth, the boy presented bilateral hip dislocation that was treated by the pediatrician and orthopedist. Motor development was mildly delayed: the child acquired supported walking by 15 months of age and unsupported walking by 21 months of age. From the age of two years, frequent falls and a difficulty for running and climbing stairs were noted by the parents and other relatives. Language and mental development were normal. Our first examination at 4 years of age revealed, a mild to moderate difficulty for getting up from the floor, a mild proximal weakness of the four limbs (MRC 4), a marked generalized hypotonia, as well as a striking and widespread joint hyperextensibility. Deep tendon reflexes were hypoactive. On physical examination lumbar lordosis and a few small areas of abnormal hypochromic pigmentation in the skin of the lower limbs were noted. Serum creatine kinase levels were two-fold increased and electromyography denoted abnormal myopathic pattern of muscle discharges. A muscle biopsy was performed at 5 years and 2 months of age and revealed mild to moderate dystrophic changes represented by size fiber variability, moderate perimysial fibrous infiltration, mild endomysial fibrous infiltration, a scarce fatty deposition and some necrotic fibers. Cardiac evaluation was normal. After a follow-up of 39 months, the course can be considered slowly progressive as we observed a worsening of proximal muscle weakness (MRC 3 to 4) and the installation of mild distal weakness (MRC 4). The joint hyperlaxity persists and the boy did not develop any joint contracture. A molecular study of the patient's DNA was done at the Department of Dermatology and Cutaneous Biology, Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, by Pan et al.[7] and demonstrated a Bethlem myopathy heterozygous in-frame deletion in the COL6A1 gene, that had been previously described[10,11]. The patient's father has normal posture, mus-

Table 1. Immunohistochemical analysis of the muscle samples of the two patients.

Patient	γ 2-LM 80 kd	γ 2-LM 300 kd	Col VI	Dys-C	γ -SG	γ -SG	γ -SG	γ -SG	γ -DG	γ -DG
1	P	P	-	P	weak	P	P	P	P	weak
2	P	P	-	P	P	P	P	P	P	P

LM, laminin; col, collagen; dys, dystrophin; SG, sarcoglycan; DG, dystroglycan; P, positive immunoreactivity, absent immunoreactivity.

cular strength and tendon reflexes but presents moderate hyperlaxity of both thumbs, the left hand fingers and the left elbow. The analysis of his DNA did not reveal any mutation.

Case 2 – A 6-year-old boy was born at term following an uneventful pregnancy from non consanguineous parents who had already two healthy children. The child presented from birth severe congenital hypotonia and generalized muscle weakness with proximal predominance. Motor development was delayed: he sits without support by the age of one year and never acquired independent walking. Language and mental development were normal. From the second year of life he gradually developed elbows and knees contractures. Our first examination at 6 years of age revealed decreased muscular strength [score of 3 and 2, following the Medical Resource Council (MRC) scale, respectively in the distal and proximal segments of the 4 limbs] widespread muscular hypotonia and hypotrophy, distal joints hyperlaxity, as well as absent deep tendon reflexes. We noted a mild ankles protrusion which the parents referred as more pronounced in the past years. The mother considered, after being inquired, that the child has hyperhidrosis when compared to his two normal older siblings. Cardiac evaluation was normal. Serum creatine kinase levels were normal and electromyography revealed abnormal myopathic pattern of muscle discharges. The first muscle biopsy, performed at the age of 6 years, showed moderate size fiber variability, and mild to moderate perimysial as well as endomysial fibrous infiltration. A second biopsy was performed at 9 years of age and evidentiated marked worsening of the former aspects and an additional accentuated fatty deposition, as well as some necrotic fibers. Immunohistochemical analysis with different antibodies was done (Table 1) and showed no collagen VI immunoreactivity (Fig 1). In a previous study[13], the patient's muscle sample had also been analysed for lamininsγ 1,γ1,γ2 and γ1 chains immunoreactivity. The result was normal, i.e. negative immunomarcation for γ 1 laminin chain, striking immunomarcation for γ 1 and γ1 laminin chains and a little less pronounced immunomarcation for γ 2 laminin chain. Along the 8 years of follow-up, the boy manifested a progressive worsening, that was characterized by an accentuation of the hipotrophy and of the contractures which became widespread, as well as by the installation of scoliosis. Currently, the boy is 14-year-old and depends on ventilatory support from 11 years of age. A molecular analysis was performed at the Department of Dermatology and Cutaneous Biology, Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, by Pan et al.[7] and revealed a de novo in-frame heterozygous deletion of the COL6A1 gene.

DISCUSSION

Collagen VI is a protein that provides a microfilamentous network in the extracellular matrix of the muscular tissue, as well as in other organs. It is essential for the correct function of muscle fibers, maintaining its structural integrity. An animal model of human Bethlem myopathy was already described and the details about the composition and the role of collagen VI have been widely discussed[3].

Bethlem myopathy and Ullrich CMD result from molecular changes in each one of the three genes encoding collagen VI. The exact mechanism by which collagen VI leads to the myopathy is not

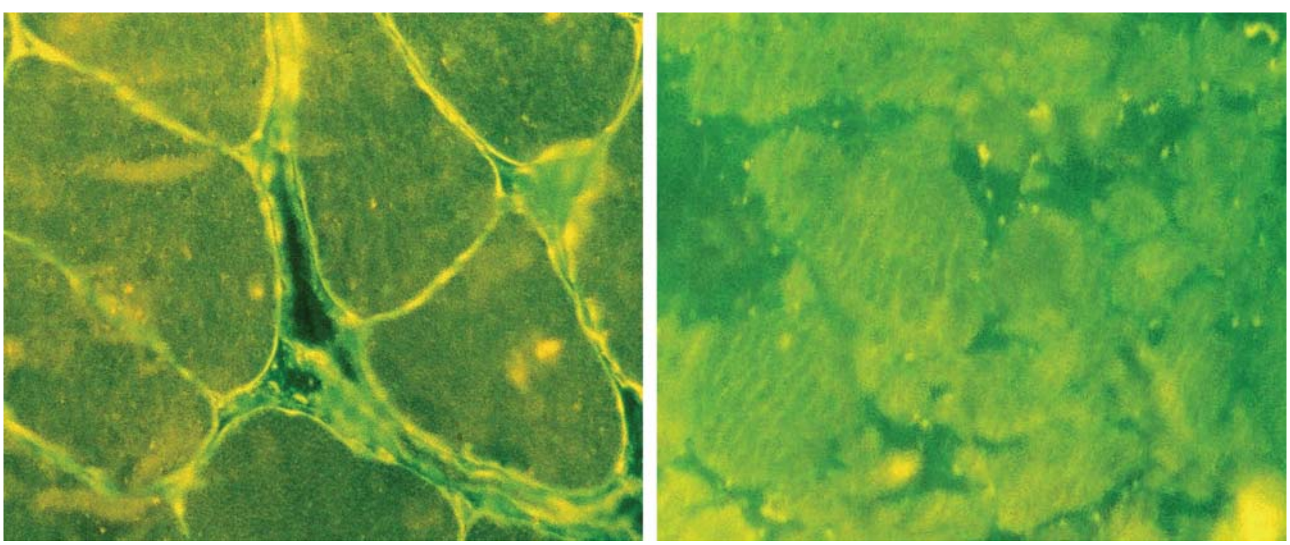

Fig 1. Immunohistochemical analysis of collagen VI in muscles samples, utilizing Hybridoma Bank antibody, code 5C6,1/100. On the left: normal contral. On the rigth: muscular biopsy of patient 2.

perfectly clear. Recently, a possible mitochondrial dysfunction in myofibers has been implicated in this mechanism[14]. According to Mercuri et al.[15], collagen VI involvement is associated to molecular changes in collagen VI genes in near to 40% of the CMD patients with Ullrich phenotype. In addition, there are reports of patients with low collagen VI reactivity without mutations in collagen VI genes[15], as well as of patients with mutations in collagen VI genes without changes in collagen VI reactivity[16], therefore documenting the genetic heterogeneity of Ullrich phenotype. Although the role of collagen VI seems be excluded in a number of cases[15], Ishikawa et al.[17] recently considered that in patients with Ullrich phenotye who have no mutations in the collagen VI genes and therefore a normal amount of Collagen VI in the interstitium, a primary abnormality of other not yet identified molecules could cause a failure of collagen VI to anchor the basal lamina to the interstitium.

The first description of Bethlem myopathy was referred by Bethlem & van Wijngaarden[18], who in 1976 reported 28 patients from three families with an autosomal dominant, benign and slowly progressive myopathy. The most characteristic aspect of Bethlem myopathy is the occurrence of early contractures of the interphalangeal joints and the elbows. Merlini et al.[19] considered that the fingers contractures are the hallmark of Bethlem myopathy. Clinical presentation and age of onset are highly variable[3,5] and although the clinical course of the disease is thought to be benign, some reports emphasize that Bethlem myopathy can be slowly progressive and can culminate in wheelchair use[20-22]. Histopathological findings were either nonspecific or compatible with dystrophic changes and creatine kinase levels can be normal or mildly elevated[3]. Collagen VI can be normal[3]. As different kinds of mutations have been found in Bethlem myopathy, there are attempts of establishing genotype/phenotype correlation in Bethlem patients and some data indicate that large deletions and mutations inside the triple-helical collagen VI monomer helix formed by the three collagenous polypeptides $\gamma 1$, $\gamma 2$ and $\gamma 3$ are associated with a more severe phenotype than those occurring in the N-terminal globular region[4].

The first report of Ullrich phenotype occurred in 1930 by Ullrich[23] who named it scleroatonic form of CMD and until 2002 only recessive mutations had been described in patients with UCMD[3,6]. In 2003, the first dominantly acting mutation in the COL6A1 gene was found in one of our Brazilian patients who we are now reporting[7] and recently more three patients with a dominantly acting mutation in the COL6A1 gene were published[8]. Beside the genetic heterogeneity, UCMD also exhibits clinical heterogeneity[4,9,15-16,24] that is not related to each of the 3 loci, but can be associated to the degree of the deficiency of collagen VI in muscle or cultured fibroblasts[16]. A complete deficiency has been observed in the severe cases while the milder ones show a partial deficiency[16]. However, the majority of patients have a severe involvement that includes scoliosis, failure to thrive, and early and severe respiratory impairment by the end of the first decade of life[15]. Mildly affected patients can be related to mutations leading to a partial deficiency of collagen VI[9,16].

The present report intends to emphasize the wide spectrum of phenotypes that can be associated to collagen VI deficiency. Both patients have marked distal hyperlaxity, and histopathological dystrophic pattern, but clinical involvement was essentially different: the first (with 3 years and 4 months of follow-up) acquired independent walking and shows a mild difficulty for running and climbing; the second (with 8 years of follow-up) never acquired independent walking and needs intermittent ventilatory support from the beginning of the second decade of life. A molecular study of both patients was performed by Pan et al.[7] at the Thomas Jefferson University and demonstrated in each one a different type of deletion of COL6A1 gene: in the first a heterozygous in-frame deletion in the COL6A1 that has been previously described in Bethlem myopathy[10,11] and in the second a dominantly acting mutation in the COL6A1 gene, that has not been described yet. This gene had been previously associated only to Bethlem myopathy and from 2003 is associated also to UCMD, as well as with a particular aspect of ossification of the posterior longitudinal ligament of spine in some subjects[25].

In Patient 1, the absence of contractures, the marked joint hyperlaxity, and the dystrophic pattern found on muscle biopsy had been supposed by us as suggestive of a non specific merosin-positive CMD diagnosis. The result of the molecular analysis denoting a previously described Bethlem myopathy heterozygous in-frame deletion in the COL6A1 gene[10,11] indicates that the boy, currently young, will probably manifest contractures and develop along the follow-up a phenotype more compatible with Bethlem myopathy. However, as his follow-up is now completing three years, he can be considered an atypical case. During the 100th European Neuromuscular Center (ENMC) international workshop[4], Muntoni considered that joint laxity, affecting especially the knees and elbows, can be a common finding at presentation and diseappears along the years. In the same opportunity[4], this author reported a case particularly coincidental to ours including by the presence of bilateral hip dislocation. His patient, currently aged 28, has also congenital torticollis, a finding that has been commonly described[3]. In addition, the dystrophic changes on the muscular biopsy, previously considered non compatible with Bethlem myopathy[26], have been found so frequently as the non specific changes[3]. However, even considering that the lack of contractures and the dystrophic changes on muscular biopsy, as observed in our Patient 1, have been reported in patients with confirmed molecular diagnosis of Bethlem myopathy[3,4] such findings at presentation can not be considered typical. In fact, Jobsis et al.[20] followed-up 23 children and 36 adult patients with Bethlem myopathy and found that nearly all children exhibit weakness or contractures during the first two years of life. In addition, according to Bertini and Pepe[5], muscle biopsy from Bethlem cases shows non specific changes and an increase of endomysial connective tissue is rarely observed. Mercury et al.[21] reported that the degree of muscle involvement varies according to the degree of motor impairment. Therefore in Patient 1 a less amount of muscle changes would be expected. In addition, as in our patient was found a heterozygous in-frame deletion of 18 aminoacids somewhat downstream in the triple-helical domain, a result of exon 14 skipping in the COL6A1 gene[7], we could theoretically expect a more severe clinical involvement. The patients already reported with a type of mutation similar to that observed in our patient have either a typical clinical picture with finger contractures[10] or a severe course when compared to that of other reported Bethlem myopathy families[11]. In one familiy one of the affected members had lost the deambulation at the age of 35 years and another member had developed Achilles' tendons bilateral shortening and finger contractures from 7 years of age[11]. Finally, as muscle immunohistochemistry with Col VI antibodies can be normal in the muscle[3], being detected only by fibroblast culture, that is not a routine procedure, the description of the clinical findings of our Patient 1 intends to emphasize that Bethlem myopathy should be included among the differential diagnosis of merosin-positive CMD. Besides this, in sporadic patients with clinical and histopathological findings suggestive of merosin-positive CMD, who also manifest joint hyperlaxity, a molecular analysis looking for Bethlem mutations is recommended.

Patient 2 has a classic severe form of UCMD and represented the first example of UCMD with a heterozygous in-frame deletion in COL6A1[7], therefore increasing the already marked genetic heterogeneity observed in this form of CMD. Very recently more three patients with dominant mutations have been described, all manifesting severe phenotype characterized by marked restriction of respiratory function, scoliosis and lack of independent ambulation in one of them[8]. According to Baker et al.[8], these new genetic data in UCMD[7-8] highlighted the necessity of a careful mutation investigation for providing an accurate genetic counseling advice. Patient 2 was the only who presented a typical severe Ullrich phenotype among around 80 childrens with clinical and histopathological diagnosis of CMD, including 34 typical MD-CMD cases, who we have attended and followed-up since 1990 at our institution. Therefore, although Muntoni and Voit[9] have referred that UCMD is probably the second most frequent variant of CMD, it is our impression that UCMD is not so common among Brazilian patients.

In conclusion, the new molecular data seem suggest that new phenotypes linked to collagen VI unit and particularly to COL6A1 gene can be identified in a next future, so defining if Ullrich and Bethlem phenotypes are independent entities or, as reported by Bertini and Pepe[5], represent an overlap between the clinical phenotypes and the molecular defects. A probable overlap between UCMD, Bethlem myopathy and Ehlers-Danlos syndromes has been the focus of recent reserches[4,9,27]. The search for new mutations in the three genes of collagen VI unit in all patients with typical Ullrich phenotype, typical Bethlem phenotype and non specific merosin-positive CMD phenotype associated to joint hyperlaxity, as well as the description of each phenotype associated to the new mutations represent an enormous field of researches in infantile myology, particularly for clarifying undefined merosin-positive CMD forms. In addition, new molecular and clinical descriptions are needed for reaching a better understanding of the role of collagen VI in the muscle function and its correlation with the other collagen units.

Acknowledgements – We are grateful to Dr. Carsten G. Bonnemann who kindly provided the molecular analysis of the patients and to Dr. Stephan Kroger for his generous gift of the antibody to collagen VI.

REFERENCES

1. Jobsis GJ, Keizers H, Vreijling JP, et al. Type VI collagen mutations in Bethlem myopathy, an autosomal dominant myopathy with contractures. Nat Genet 1996;14:113-115.
2. Speer MC, Tandan R, Rao PN, et al. Evidence for locus heterogeneity in the Bethlem myopathy and linkage to 2q37. Hum Mol Genet 1996; 5:1043-1046.
3. Pepe G, de Visser M, Bertini E, et al. Bethlem myopathy (BETHLEM) 86th ENMC international workshop, 10-11 November 2000, Naarden, The Netherlands. Neuromuscul Disord 2002;12:296-305.
4. Pepe G, Bertini E, Bonaldo P, et al. Bethlem myopathy (BETHLEM) and Ullrich scleroatonic muscular dystrophy: 100th ENMC international workshop, 23-24 November 2001, Naarden, The Netherlands. Neuro muscul Disord 2002;12:984-993.
5. Bertini E, Pepe G. Collagen type VI and related disorders: Bethlem myopathy and Ullrich scleroatonic muscular dystrophy. Eur J Paediatr Neurol 2002;6:193-198.
6. Camacho Vanegas O, Bertini E, Zhang RZ, et al. Ullrich scleroatonic muscular dystrophy is caused by recessive mutations in collagen type VI. Proc Natl Acad Sci USA 2001;98:7516-7521.
7. Pan TC, Zhang RZ, Sudano DG, Marie SK, Bonnemann CG, Chu ML. New molecular mechanism for Ullrich congenital muscular dystrophy: a heterozygous in-frame deletion in the COL6A1 gene causes a severe phenotype. Am J Hum Genet 2003;73:355-369.
8. Baker NL, Morgelin M, Peat R, et al. Dominant collagen VI mutations are a common cause of Ullrich congenital muscular dystrophy. Hum Mol Genet 2005;14:279-293.
9. Muntoni F, Voit T. The congenital muscular dystrophies in 2004: a century of exciting progress. Neuromuscul Disord 2004;14:635-649.
10. Lamande SR, Shields KA, Kornberg AJ, Shield LK, Bateman JF. Bethlem myopathy and engineered collagen VI triple helical deletions prevent intracellular multimer assembly and protein secretion. J Biol Chem 1999;274:21817-21822.
11. Pepe G, Giusti B, Bertini E, et al. A heterozygous splice site mutation in COL6A1 leading to an in-frame deletion of the alpha1(VI) collagen chain in an Italian family affected by Bethlem myopathy. Biochem Biophys Res Commun 1999;258:802-807.
12. Ferreira LG. Análise imunohistoquímica das proteínas do complexo distrofina-glicoproteínas associadas em pacientes com distrofia muscular congênita. Tese., São Paulo, 2002.
13. Reed UC. Distrofia muscular congênita: estudo da variabilidade fenotípica e análise da correlação clínico-imunohistoquímica. Tese. São Paulo, 1999.
14. Irwin WA, Bergamin N, Sabatelli P, et al. Mitochondrial dysfunction and apoptosis in myopathic mice with collagen VI deficiency. Nat Genet 2003;35:367-371.
15. Mercuri E, Yuva Y, Brown SC, et al. Collagen VI involvement in Ullrich syndrome: a clinical, genetic, and immunohistochemical study. Neurology 2002;58:1354-1359.
16. Demir E, Ferreiro A, Sabatelli P, et al. Collagen VI status and clinical severity in Ullrich congenital muscular dystrophy: phenotype analysis of 11 families linked to the COL6 loci. Neuropediatrics 2004;35:103-112.
17. Ishikawa H, Sugie K, Murayama K, et al. Ullrich disease due to deficiency of collagen VI in the sarcolemma. Neurology 2004;62:620-623.
18. Bethlem J, Wijngaarden GK. Benign myopathy, with autosomal dominant inheritance. A report on three pedigrees. Brain 1976;99:91-100.
19. Merlini L, Morandi L, Granata C, Ballestrazzi A. Bethlem myopathy: early-onset benign autosomal dominant myopathy with contractures: description of two new families. Neuromusc Disord 1994;4:503-511.
20. Jobsis GJ, Boers JM, Barth PG, de Visser M. Bethlem myopathy: a slowly progressive congenital muscular dystrophy with contractures. Brain 1999;122:649-655.
21. Mercuri E, Cini C, Counsell S, et al. Muscle MRI findings in a three-generation family affected by Bethlem myopathy. Eur J Paediatr Neurol 2002;6:309-314.
22. Haq RU, Speer MC, Chu M-L, Tandan R. Respiratory muscle involvement in Bethlem myopathy. Neurology 1999;52:174-176.
23. Ullrich O. Kongenitale atonisch-sklerotische Muskeldystrophie, ein weiterer Typus der heredodegeneration Erkrankungen des nueromuskularen Systems. Z Ges Neurol Psychiat1930;126:171-201.
24. Demir E, Sabatelli P, Allamand V, et al. Mutations in COL6A3 cause severe and mild phenotypes of Ullrich congenital muscular dystrophy. Am J Hum Genet 2002;70:1446-1458.
25. Tanaka T, Ikari K, Furushima K, et al. Genomewide linkage and linkage disequilibrium analyses identify COL6A1, on chromosome 21, as the locus for ossification of the posterior longitudinal ligament of the spine. Am J Hum Genet 2003; 73: 812-822.
26. Tohyama J, Inagaki M, Nonaka I. Early onset muscular dystrophy with autosomal dominant heredity. Report of a family and CT findings of skeletal muscle. Brain Dev 1994;16:402-406.
27. Kirschner J, Hausser I, Zou Y, et al. Ullrich congenital muscular dystrophy: connective tissue abnormalities in the skin support overlap with Ehlers-Danlos syndromes. Am J Med Genet A 2004;132A:296-301.