CAZ CLINIC

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COLLAGEN VI RELATED MUSCLE DISORDER. ULLRICH CONGENITAL MUSCULAR DYSTROPHY. CASE REPORT

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REZUMAT

TULBURARE MUSCULARĂ LEGATĂ DE COLAGEN VI. DISTROFIA MUSCULARĂ CONGENITALĂ ULLRICH. RAPORT DE CAZ

Colagenul tipul VI este un colagen microfibriliar localizat in matrixul extracelular predominant de tesuturi conjuctive. Este compus din 3 lanturi α codate de trei gene independente. Mutatiile in aceste gene provoaca maladii musculare de un anumit grup care pot fi referiti ca miopatii lincate de colagenul VI. Aceste miopatii cuprind un spectru de maladii ce cuprind cazuri de la cele mai severe cazuri precum distrofia musculara congenitala Ullrich (DMCU) urmat de fenotipuri de tranzitie severa spre miopatia mai usoara Bethlem (MB). In aditie, fenotipul contractural, referit drept mioscleroza, este cunoscut si asociat cu mutatia in gena *COL6A2*. DMCU a fost initial descris intr-o serie de articole din anii 1930 de catre Otto Ullrich, care sa referit la conditie drept, distrofia musculara atonica-sclerotica cu progresul contracturilor. MB a fost descrisa in 1976 de catre Bethlem si van Wijngaarden drept o conditie autosomal dominanta gasita in 28 de indivizi din cadrul a 3 familii Olandeze, acesti indivizi avand specific contractii de flexie a degetelor.
In acest articol noi descriem un caz a unui pacient Moldovean cu fenotip clinic de DMCU si rolul colagenului VI in patogeneza acestuia.

РЕЗЮМЕ

КОЛЛАГЕНОПАТИЯ VI ТИПА. БОЛЕЗНЬ УЛЬРИХА. КЛИНИЧЕСКИЙ СЛУЧАЙ.

Коллаген шестого типа представляет собой микрофибриллярный коллаген, локализованный в матриксе большинства соединительных тканей. Он состоит из трёх альфа цепей, кодирующихся тремя отдельными генами. Мутации в этих генах приводят к заболеваниям, известным как миопатии, связанные с коллагеном шестого типа. Эти миопатии включают в себя широкий спектр заболеваний, начиная от самых тяжёлых по типу врождённой мышечной дистрофии Ульриха (ВМДУ) через серию фенотипов переходной тяжести к более лёгкой миопатии Бетлема (МБ). Также известен преимущественно контрактурный фенотип, называемый миосклерозом и связанный с мутациями в гене *COL6A2.* ВМДУ была впервые описана Отто Ульрихом в серии статей, опубликованной в 1930-х годах, где он называл её «атоническо-склеротической мышечной дистрофией» с прогрессирующими контрактурами. МБ была описана в 1976 году Бетлемом и ван Винжгаарденом как аутосомно-доминантно наследуемое заболевание. Описание было составлено на основе анализа 28 больных из трёх голландских семей, имевших сгибательные контрактуры пальцев.
В этой статье мы описываем клинический случай молдавского пациента с клиническим фенотипом ВМДУ и роль коллагена шестого типа в патогенезе болезни.

Introduction. Collagen type VI is a microfibrillar collagen found in many extracellular matrices including those of muscle, skin, tendon, and vessels. It is composed of three α chains encoded by three independent genes on chromosomes 2 and 21. Mutations in these three genes have been found to underlie a group of muscle disorders that are now referred to as collagen VI-related myopathies. These myopathies encompass a spectrum of disorders ranging from the more severe Ullrich congenital muscular dystrophy (UCMD) through transitional severity phenotypes to the milder Bethlem myopathy (BM). An additional, mostly contractural phenotype, referred to as myosclerosis, has also been delineated and associated with mutations in *COL6A2* [1]COL6A2, and COL6A3, coding for three α chains of collagen type VI, underlie a spectrum of myopathies, ranging from the severe congenital muscular dystrophy-type Ullrich (UCMD. UCMD was initially described in a series of papers in the 1930s by Otto Ullrich, who referred to the condition as "atonic-sclerotic muscular dystrophy" because of the characteristic occurrence of weakness and striking joint hypermobility ("atony" in the original description) in conjunction with significant and evolving contractures ("sclerotic"). After collagen VI mutations had been identified in BM it was the realization by Enrico Bertini and Mimma Pepe in 2001 in Italy that some of the clinical features in UCMD were reminiscent of BM that led to the first discovery of collagen VI mutations in this condition as well [2] [3]. UCMD is classically described as an autosomal recessive condition. It is a clinically and genetically distinct entity within the congenital muscular dystrophy. Bethlem myopathy was first described in 1976 by Bethlem and van Wijngaarden as an autosomal dominantly inherited mild proximal myopathy with long finger flexion contractures occurring in 28 individuals of three Dutch pedigrees [4]. In this article we present case report of Modavian's patient with clinical phenotypes of Ullrich congenital muscular dystrophy (UCMD1, MIM254090) and the role of collagen VI in causation.

Case report. Patient ***A. (P.A.),*** born at 2017 parents addressed at geneticist in center of reproductive health and medical genetics in Chisinau, Republic of Moldova when child had 2 months of age. Main accusations: weakness and spine deformation. Parents are not consanguineous. Parent's age: mother – 34 years old, father – 41 years old. Pedigree is not burdened by the maternal and paternal lines, but both parents are above average height.

It was first pregnancy, without pathologies. Was born at 39 weeks gestational age with breech presentation, was born through cesarean section. Weight after birth was 3200 gramms. Height - 56 cm. Appgar 8/8. From the birth patient had ankiloglosia, congenital hydrocele, bilateral congenital hip subluxation, muscle weakness. Vaccinated in correspondence with Republic of Moldova national vaccination plan. Feeding is natural. After the first two months added 2686 gramms of weight.

At 1 month of age parents addressed to neurologist because of torticollis and at the age of 2 moths — at geneticist. At 2 months of age: clear and palid skin, skull is brachycephalic, arachnodactylia, transverse fold of the hand, muscular torticollis at right and severe kyphoscoliosis; neurological state — pronounced hypotonia, more at upper shoulder girdle, distal upper and lower limbs muscles hypotrophy, hyporeflexia. The phenotype was suggestive of a myopathy, particularly of Ullrich Congenital muscular dystrophy (UCMD1, MIM 254090)

Biochemical blood analysis performed at 1 moth of age revealed: rised homocysteine -**10** uM (ref 3.0-6.0), total bilirubine- **58.8** (ref<20.0) uM, direct bilirubine- **8.44**(N 0.0-3.4) uM, ionic calcium, iCa^{++}- **1.43** (N 1.13-1.32) uM, potassium, K - **5.34** (N 3.5-5.3) uM, AST **118.0** (N 13.0-45.0) U/L; decreased sodium, Na-**132.80** (N 137.0-145.0) uM, pancreatic alpha(α)-amylase - **5.2** (13.0-53.0) U/L. Total calcium, Ca^{++}- 2.55(N 2.14-2.57) uM, clorine, Cl – 103.20 (N 98.0-107.0) uM, phosphorous, P- 1.98 (N1.29-2.26) uM, ALT- 60 (15.0-60.0) U/L were within reference range for corresponding age. At 2 moths remained rise of direct (13.8 uM) and total bilirubine (37,6 uM), homocysteine levels rised up to **17,5** uM. There was unsignificant rise of total creatin kynase (CK) **204,0** (ref 0.0-171.0 U/L, CK-MB 27.0 (ref 0.0-25.0) U/L; LDH was within reference range 259,0 (0-430) U/L. There was rise of CK level upto 433,0 and CK-MB up to 74,00 at the age of one year.

USG performed May 2017 (at 2 months) – size and echo structure of liver, pancreas and spleen are within corresponding age reference age. Kidneys are placed in typical place, without echoscopically determined pathologies.

NMR (Magnetom Siemens Essenza 1.5 Tesla) of the cervical, thoracic and lumbar spinal cord ("whole spine" regime, w/o contrast) performed May 2017 discovered a diffuse, fusiform, pseudotumoral formation in right m. Sternocleidomastoideus - caracteristic for fibromatosis colli. Cervico-toraco-lombar S-type scoliosis of moderate grade.

Electromyography performed May 2017- electrophysiological indexes within reference range.

At May 2017 was performed search of exons 7 & 8 deletions in *SMN1* gene using PCR-RFLP method (Chisinau, Moldova). No deletions were revealed, spinal muscular atrophy excluded.

PCR-RFLP analysis (performed in Moldova) of folate and methyonine cycles genes (*MTHFR, MTR, MTRR, CBS)* revealed heterozygous polymorphisms *MTHFR* C677T, A1298C and *MTR* A2756G, what explains high homocysteine concentration at child.

Whole-exome sequencing and data analysis was performed in University Medical Centre Hamburg-Eppendorf, Germany at June 2019. Coding regions including surrounding intronic sequences (+/-10 bp) were isolated and enriched out of the whole genome from

the three DNAs of the family proband and his parents using in-solution technology *Sure SelectXT Human Al Exon V6* (Agilent). NGS was performed by using the *Illumina HiSeq*® platform at CeGaT, Tübingen, Germany. Sequencing data were bioinformatically analyzed via *in-house* pipeline for all inheritance patterns and aligned to the human reference genome (hg19). Has been performed variant validation through PCR amplification of exon 7 of the *COL6A2* gene, exon 33 of the *RYR1* gene, exon 7 of the *SSR4* gene and exons 35 and 36 of the *EIF2AK4* gene as well as adjacent intronic sequences from the three aforementioned DNA samples. Directly sequenced the PCR products have been performed by using an automatic sequencer (Applied Biosystems ABI 3500). The obtained sequenced were evaluated by the Sequence Pilot SeqPatient Software (JSI medical systems GmbH) and compared to the reference sequences in the database (mRNA reference number: *COL6A2*, NM_001849.3; *RYR1,* NM_001204526.1; *EIF2AK4,* NM_001013703.4).

Results of Whole-exome sequencing. To identify the genetic cause of ***PA.'s*** muscular disease, have been analyzed the exomes of the family using a bioinformatics filtering for harboring *de novo* variants, which are potentially pathogenic and have not been described in the general population (dpSNP 138, 1000 Genomes Project, Exome Variant Server, ExAC browser, and gnomAD browser). This analysis lad to the identification of a missense variant in *COL6A2* (MIM 010240), the disease gene for Bethlem myopathy (BTHLM1, MIM 158810) and Ullrich congenital muscular dystrophy (UCMD1, MIM 254090). Also, had identified a second missense variant in *RYR1* (MIM 180901), the disease genefor central core disease (CCD, MIM117000), malignant hyperthermia (MIM 145600) and minicore myopatyhy with external ophtalmoplegia (MMD, MIM 255320). The genetic variants were validated in Alexandu's DNA in the heterozygous state using Sanger sequencing. Neither his mother nor his father carried the variants in the DNA. Therefore, the missense variants in *COL6A2* and *RYR1* occurred *de novo* in ***P.A.***: ***COL6A2*: c.874G>T/p.(Gly292Cys) & *RYR1*: c.4855G.A/p .(Ala1619Thr)**.

Also, have been analyzed the exome data based on an autosomal recessive inheritance model with homozygous or compound heterozygous variants and no homozygotes in ***P.A.*** The minor allele frequency of ≤0.1% in population databases (dpSNP138, 1000 Genomes Project, Exome variant Server, ExAC Browser and gnomAD Browser). ***P.A.'s*** parents are heterozygous carriers of the variants. Have been identified compound heterozygous variants in *EIF2AK4* (MIM 609280), the disease gene for *pulmonary venoocclusive disease 2* (MIM 234810). These variants were validated by Sanger-sequencing and to be in *trans* in the DNA of ***P.A.*** as his mother and father were shown to be heterozygous carriers for one of two variants.

***EIF2AK4:* c.4669C>T/p.(Arg1557*)- paternally inherited**
***EIF2AK4:* c.4646G>A/p.(Arg1549His)- maternally inherited**

Exome data were also analyzed based on an X-chromosomal inheritance model with hemizygous variants in population databases and no herizygotes in ***P.A.*** and his mother is a heterozygous carrier of the respective X-linked variant in *SSR4* (MIM 300090), the disease gene for congenital disorder of glycosylation (CDG1Y, MIM300934). The variant was validated in the hemizygous state in the DNA of ***P.A.***, and his mother is a heterozygous carrier of the variant.

***SSR4:* c.454A>G/p.(Thr152Ala) – X-linked, maternaly inherited**

Discussion. By molecular genetic analysis have been identified the heterozygous ***de novo* missense variant** c874G.T/p (Gly292Cys) in the gene *COL6A2*, in which heterozygous or biallelic variants cause BTHLM1 and UCMD1. Based on database and literature searches we interpret this variant to be the main genetic cause for the observed muscular disease in ***P.A.***. The identified *de novo* missense variant c.874G>T/p.(Gly292Cys) is predicted to be damaging by all pathogenicity prediction programs. Heterozygous variants in *COL6A2* are associated with autosomal dominant BTHLM1 autosomal dominant UCMD1. Bethlem and van Wijngaarden (1976) described the phenotype of Bethlem myopathy (BM) as a benign myopathy with an early infancy onset and slow progression. Constant findings in patients are moderate weakness, atrophy of trunk and limb muscles, early flexion contractures of elbows and interphalangeal joints of the last four fingers, and planter flexion contractures of the ankles. In comparison, the haalmarrks of UCMD are muscle weakness of early onset with proximal joints contractions and striking hyperelasticity of distal joints and normal intelligence [4]. The observed kyphoscoliosis in ***P.A.*** is found in pationts with UCMD1 and has been reported as a typical feature of UCMD1 [5]. ***P.A.***'s phenotype shows overlap with both forms of *COL6A2*-related myopathies.

COL6A2 encodes the α2 chain of collagen VI. Collagen VI consists of three district α-chains (α1, α2, α3). All three chains contain a central short triple helical domain of 335 to 336 amino acids with repeating Gly-Xaa-Yaa sequences, flanked by two large N- and C-terminal globular domains made up of motifs of 200 amino acids each, which are homologous to von Willebrand factor (vWF) type A domains 60–64 (Fig. 1). *COL6A1*, which consists of 37 exons (35 coding), contains one promoter 65 and produces a single transcript (NM_001848) encoding a protein of 1021 amino acids (NP_001839) with two C-terminal and one N-terminal vWF type A-like domains [4]. Alteretion within Gly-Xaa-Yaa triplets descript the multimerization of collagenVI into microfibrila [6]

Disease-associated amino acid subsitutions affecting Cly292 are listed in the HGMD database: c.875G>A/p.(Gly292Asp), c874G>A/p.(Gly292Ser), c.875G>T/p.(Gly292Val). These domimant variant have been associated with intermediate and moderate progressive forms of UCMD1 [6][7][8].

Autosomal dominantly acting missense variant associated with UCMD1 mainly cluster in the T-terminal region of the triple helical domain (TH) (Fig.1). The indentified variant p.(Gly292Cys) most likely disrupts one Gly-Xaa-Yaa triplet in the highly conserved TH domain. Heterozygous glycine substitution have been reported in early-severe UCMD phenotyps(c.833G>T/p.Gly278Val; c.850G>A/p.Gly284Arg; c.887G>T/p.Gly296Val) [7], however, clinica; variability ranges from severe UCMD1 and intermediate to mild BTHLM1 phenotypes [4], [6]

The identified amino acid substitution p.(Gly292Cys) in ***P.A.*** is located in triplet 13. Pace et al. have suggested that patients with glycine substitutions in a critical region including Gly-X-Y triplets 10-15 have a more severe disruption of collagen VI assembly and a more severe clinical phenotype [9] because to be of particular impotance for microfibril formation. In Butterfield's cohort, patients with mutations inside the critical region tend to a more severe phenotype with 48% ES-UCMD or typical UCMD compared to 23% ES-UCMD or typical UCMD in cases with mutations outside the critical region. Patients with glycine substitutions outside the critical region tended toward a milder phenotype with 40% BM compared to 7% BM in patients with mutations inside the critical region [6]

In addition, have been identified variants of unknown significance (VUS) in two disease genes:

- A de novo missense variant of unknown significance in the disease gene *RYR1*
- And compound heterozygous variants in *EIF2AK4*, one likely pathogenic allele and a second variant which were interpret as VUS

The heterozygous de novo *RYR1*variant c.4855G>A predicts the amino acid subctutution p.(Ala1619Thr), and three of six pathogenicity prediction programs (CADD, REVEL, M-CAP, SIFT, Polyphen2 and MutationTaster) predict the variant to be possibly damaging.

Ryanodine receptor gene (*RYR1*) mutations have been associated withare associated with two different neuromuscular disorders: central core disease (CCD) and multiminicore/minicore/multicore disease (MmD), and susceptibility to malignant hyperthermia (MH). *RYR1* encodes the principal sarcoplasmic reticulum calcium release channel and has been implicated in various congenital myopathies [9].

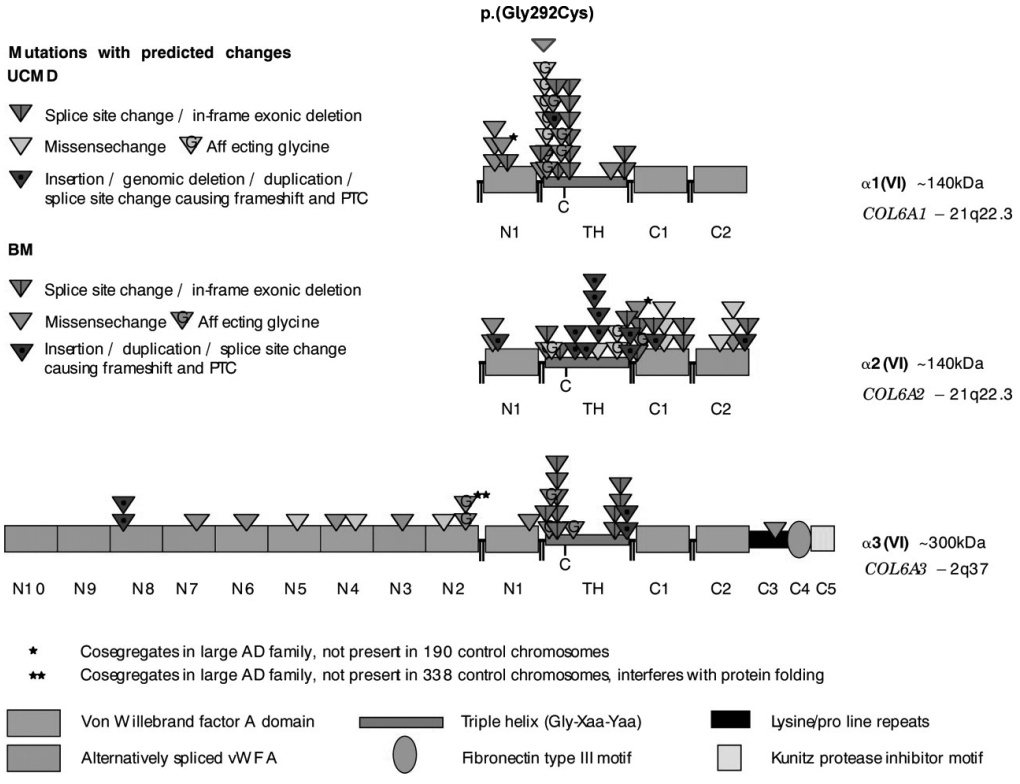

Fig.1. ***Genomic organisation of collagen VI and localisation of genomic changes reported for BM and UCMD to date; modification from Chu et al. The triple helical domains contain a single cysteine residue (depicted as "C") which is important for dimer assembly. The localisation of the genomic changes reported for BM and UCMD to date is shown stratified by clinical phenotype.The p.(Gly292Cys) change identified in P.A. is indicated in orange. Figure adapted from Lampe and Bushby (2005) [4].***

CCD is caused by heterozygous or bialelic variant in *RYR1*, while MMD is an autosomal resessive disorder. The disease-associated variants cluster in three mutational hotspot regions of *RYR1* [10]the molecular causes remain unknown for nearly half of the patients, due to genetic heterogeneity and conventional molecular diagnosis based on a gene-by-gene approach. We aimed to test next generation sequencing (NGS The variant found in ***P.A.***'s DNA, c.4855G>A, is located in exon 33, which is outside the three mutation clusters. CCD is a relatively mild congenital myopathy, characterized by developmental delay and mild proximal weakness, most pronounced in the hip-girdle muscular. Orthopedic complications, including dislocation of hips and scoliosis, are common. The Phenotype of ***P.A.*** shows some overlap with CCD.

Biallelic variants in the eukaryotic initiation factor 2 alpha kinase 4 (*EIF2AK4*) gene cause heritable pulmonary veno-occlusive disease (PVOD)/pulmonary capillary haemangiomatosis (PCH), a rare cause of pulmonary hypertension [11], that is characterized histologically by widespread fibrous intimal proliferation of septal veins and preseptal venules and is frequently associated with pulmonary dilatation and proliferation. Penetrance is unknown [12]. PVOD/PCH due to *EIF2AK4* mutations can occur from birth to age 50 years (median 26 years (range 0-50.3))[13]. Multiple disease causing variants have been identified in patients with PVOD. The majority of disease-relevant variants are truncating or insertion/deletion variants which are predicted to disrupt protein function [11].

The paternally inherited nonsense variant c.4669C>T/p.(Arg1557*) has s worldwide allele frequency of 0,000012 (three heterozygous carriers in gnomAD browser). The variant is not listed as a known disease causing variant in the HGMD database or the ClinVar database. Nometheless, this variant likely represents a loss-of –function variant and therefore a pathogenic allele. The maternally inherited missense variant c.4646G>A predicts the amino acid substitution p.(Arg1549His) and is predicted to be possibly damaging by four of six *in silico* tools (CADD, REVEL, M-CAP, SIFT, POlyPhen2 and MutationTaster). The missense variant has a worldwide allele frequency of 0,000785, which represents 22 heterozygous carriers in gnomAD browser. To rule out an effect on splicing by the missense variant, splice site predictions were performed. The four programs did not predict an alteration of *EIF2AK4* pre-mRNA splicing.

The c.4646G>A variant has been observed in an individual with primary pulmonary arterial hypertension (PAH) in the heterozygous state. However, whether heterozygous EIF2AK4 variants contribute to the aetiology of PAH is currently unclear [12],[13].

Also, a hemizygous variant c.454A>G in *SSR4* gene indentified in ***P.A.*** could be interpret as a likely benign variant for the following reasons: This variant predicts the amino acid substitution p,(Thr152Ala). Only one of six pathogenicity prediction programs (CADD, REVEL, M-CAP, SIFT, Polyphen2 and Mutation Taster) predicts the variant to be possibly damaging. Variants in SSR4 are associated with CDG1Y. SSR4-CDG is a form of congenital disorders of N-linked glycosylation characterized by neurologic abnormalities (global developmental delay in language, social skills and fine and gross motor development, intellectual disability, hypotonia, microcephaly, seizures/epilepsy), facial dysmorphism (deep set eyes, large ears, hypoplastic vermillion of upper lip, large mouth with widely spaced teeth), feeding problems often due to chewing difficulties and aversion to food with certain textures, failure to thrive, gastrointestinal abnormalities (reflux or vomiting) and strabismus [14]. This phenotype (except hypotonia) does not overlap with the phenotype of ***P.A.***.

Conclusion. Have been indentified the *de novo* missense variant **c.874G>T/p.(Gly292Cys)** in *COL6A2* gene. Due to known disease-associated variants in *COL6A2* (affecting the same codon), the reported genotype-phenotype correlation, and ***P.A.***'s phenotype this variant most likely underlies his muscular process. In addition, have been identified variants of unknown significance in two additional disease genes. Whether or not these variants contributed to ***P.A.***'s current phenotype or will cause other clinical features in the future cannot be predicted to date:

1. The heterozygous *de novo RYR1* missense variant c4855G>A/ p.(Ala1619Thr) could not exclude a possible association of this variant with malignant hyperthermia. That is why, we prophylactically recommended to avoid any anesthetic agent know to trigger malignant hyperthermia, which seems to be even more important because of the proven neuromuscular disorder of ***P.A.***
2. The likely pathogenic, paternally inherited variant c.4669C.T/p.(Arg1557*) and the maternally inherited variant of unknown significance c.4646G>A/ P.(Arg1549His) in *EIF2AK4* although show a prediction to PVOD, which is currently not proven. But we recommended regular respective clinical investigations in ***P.A.*** and will perform multiple isoelectric focusing for determination abnormal/ normal carbohydrate deficient transferrin profile and electrospray mass spectrometry analyses.

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