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"BIOCHEMICAL MARKERS OF AMYOTROPHIC LATERAL SCLEROSIS AND THEIR SIGNIFICANCE. PROGNOSIS AND CONSEQUENCES OF THE DISEASE"

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Annotation: *In this article, amyotrophic lateral sclerosis is one of the diseases whose etiopathogenesis and treatment methods have not been fully studied worldwide. Early detection of biochemical markers of the disease of YoAS among the population, slowing down the development of the disease and prevention of its consequences are considered*

Keywords: *ALS, ,BM, FTD, SOD1, TARDBP, TBK1, FUS, PFN1, DCTN1, MuSK*

"YON AMIOTROFIK SKLEROZ KASALLIGINING BIOKIMYOVIY MARKYORLARI VA ULARNING AHAMYATI. KASALLIKNING PROGNOZI HAMDA OQIBATLARI"

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Annotatsiya: Ushbu maqolada Yon amiotrofik skleroz dunyo miqyosida etiopatogenezi va davolash usullari to'liq o'rganilmagan kasalliklardan biri hisoblanib, aholi o'rtasida YoAS kasalligini biokimyoviy markyorlarini erta aniqlash, kasallikning rivojlanishining sekinlashtirish va oqibatlarini oldini olishdagi o'rni ko'rib chiqiladi

Kalit so'zlar: YoAS,BM, FTD, SOD1, TARDBP, TBK1, FUS, PFN1, DCTN1, MuSK

«БИОХИМИЧЕСКИЕ МАРКЕРЫ БОКОВОГО АМИОТРОФИЧЕСКОГО СКЛЕРОЗА И ИХ ЗНАЧЕНИЕ. ПРОГНОЗ И ПОСЛЕДСТВИЯ ЗАБОЛЕВАНИЯ»

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Аннотация: *В данной статье боковой амиотрофический склероз является одним из заболеваний, этиопатогенез и методы лечения которого во всем мире до конца не изучены. Рассмотрены раннее выявление биохимических маркеров заболевания БАС среди населения, замедление развития заболевания и профилактика его последствий.*

Ключевые слова: *БАС, FTD, SOD1, TARDBP, TBK1, FUS, PFN1, DCTN1, MuSK*

Background: Amyotrophic Lateral Sclerosis (Amyotrophic Lateral Sclerosis) was first identified by Jean-Martin Charcot in 1869 as a pure motor neuron disease, but is now recognized as a multisystem neurodegenerative disease with clinical, genetic and neuropathological heterogeneity [1-3]. The clinical presentation of YoAS is usually focal muscle weakness in adults and tends to spread as the disease progresses. Weakness often begins in the muscles of the limbs, often in the distal muscles rather than the proximal muscles. About 25% - 30% of cases begin in the bulbar form of the disease, which is manifested by dysarthria, dysphagia, dysphonia, or rarely, weakness of the masticatory muscles. There is a high degree of variability in the age of onset, site of onset, and disease progression of YoAS. The disease is relentlessly progressive in most patients, with a median survival of approximately 3 years after the onset of symptoms, where death is primarily due to respiratory failure. Approximately 50% of patients suffer from some degree of additional extra-motor manifestations in addition to motor problems. At the genetic level, there is considerable disease heterogeneity, with more than 20 genes associated with YoAS. The five most common genetic causes are hexanucleotide expansion in chromosome 9 open reading frame 72 (C9orf72) and superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TARDBP), sarcoma (FUS), and TANK-binding kinase 1 mutations. (TBK1). Together, they account for approximately 15% of all patients [1-3].

The most common neuropathological hallmark of YoAS is the cytoplasmic accumulation of the TARDBP-encoded protein TDP-43, which is found in more than 95% of YoAS cases [7]. TDP43 is an RNA and DNA binding protein involved in many processes including transcription, splicing, microRNA maturation, RNA transport, and stress granule formation. Consistent with its nuclear and cytoplasmic functions, TDP-43 can shuttle between the nucleus and cytoplasm, but its localization is predominantly nuclear. Cytoplasmic mislocalization leads to nuclear disappearance of TDP-43 and accumulation of cytoplasmic proteins, which is a hallmark of YoAS.TDP-43 inclusions are not specific to patients with TARDBP mutations , but also in patients with C9orf72 expansions or TBK1 mutations and in patients with sporadic YoAS (sYoAS). TDP-43 is predominantly localized in the nucleus under basal conditions, but in YoAS it is mislocalized and phosphorylated in the cytoplasm to form aggregates. Other aggregated proteins such as SOD1 and FUS are found in patients with SOD1 and FUS mutations, respectively. Patients with the C9orf72 hexanucleotide repeat expansion accumulate proteins with a dipeptide copy translated from GGGGCC copies, when the copy is located in a non-coding region of the gene[8]. In the pathogenesis of YoAS, there are many molecular factors such as proteostasis disturbance, excitotoxicity, neuroinflammation, mitochondrial dysfunction and oxidative

stress, oligodendrocyte dysfunction, cytoskeletal disorders and axonal transport defects, NA-transport disorder, nuclear metabolism disorder, NA-phytotoxicity, NA-phytostatic dysfunctions, NA-tissue disturbance. roads involved. repair [2,12]. Interestingly, many genes associated with YOAS appear clustered in key pathways: protein quality control and degradation, RNA metabolism, and cytoskeletal and axonal transport.

The purpose of the study: to determine the clinical significance of the biomarkers specific for YoAS and whether they play an important role in the progression of the disease.

Violation of proteostasis. Protein aggregates or their oligomeric complex precursors disrupt normal protein homeostasis and cause cell stress. Molecular chaperones can help refold misfolded proteins, but when the cell is overloaded with misfolded proteins, it is targeted for degradation after ubiquitination by the ubiquitin-proteasome system. Alternatively, protein aggregates may undergo lysosomal degradation by autophagy after binding to p62 (sequestosome 1). Several YoAS-related genes play important roles for protein accumulation and impaired degradation as key factors in the pathogenesis of YoAS. ubiquilin-2 (UBQLN2) plays a role in the delivery of ubiquitinated proteins to the proteasome [10]. There are several other mutations in genes involved in identifying cargo for the autophagy pathway, as they encode proteins that interact with ubiquitinated cargo and the phagophore membrane: SQSTM1 (encodes the p62 protein that directs ubiquitinated proteins to the phagophore) [12], optineurin (OPTN, which acts as a receptor for autophagy) [11], TBK1 (which activates OPTN by phosphorylation) [13], valosin-containing protein (VCP) [9] and C9orf72 protein [10].

Disruption of RNA metabolism. Many RNA binding proteins are involved in the pathogenesis of YoAS. The identification of mutations in the genes of two related RNA-binding proteins, TDP-43 and FUS, introduced a dysregulation mechanism of RNA metabolism for YoAS [10]. Additional mutations in other RNA-binding proteins such as angiogenin (ANG), senataxin (STX), matrin-3 (MATR3), heterogeneous nuclear ribonucleoproteins A1 (hnRNPA1) and A2B1 (hnRNPA2B1), and ataxin-2 (ATXN2) are associated with impaired RNA metabolism. , the notion that it probably plays an important role in YOAS [11]. Under normal conditions, these proteins are mainly located in the nucleus, where they perform important functions in transcription, splicing, noncoding RNA metabolism, and microRNA biogenesis. Hence, nuclear depletion may be deleterious and induce gross transcriptome abnormalities. Cytoplasmic mislocalization with aggregation can also cause toxicity.

Cytoskeletal disorders and axonal transport defects. Several genetic factors in YoAS point to the importance of cytoskeletal integrity and axonal transport [12]: mutations in profilin-1 (PFN1) and tubulin alpha-4A (TUBA4A) rarely cause YoAS, but destabilization of the tubulin network and axonal transport deficits was found to cause deficits. The dynactin complex is an important activator of the dynein motor that stabilizes cargo binding and modulates motor function. Point mutations in the gene encoding the dynactin1 (DCTN1) subunit of the dynactin complex can cause YoAS or FTD [12]. Mutations in the C-terminus of kinesin-1, encoded by the kinesin heavy chain 5A (KIF5A) isoform, can disrupt the anterograde transport of cargo along microtubules [7].

Inspections. Biomarkers can play a crucial role in diagnostic, prognostic or predictive research. They may be of potential value for stratifying patients and monitoring treatment effects in clinical trials. Although not yet integrated into standard clinical practice, several biomarkers such as cerebrospinal fluid neurofilament levels (specifically the heavy subunit of phosphorylated neurofilament) are useful in supporting the diagnosis [7], especially in recent-onset muscle weakness, central motor patients with no obvious signs of neuronal involvement or with concomitant neuropathy/plexopathy/cervical myelopathy often undergo magnetic resonance imaging of the brain and spinal cord to rule out systemic lesions affecting the motor system [9]. In addition, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography can reveal the typical pattern of hypometabolism and frontotemporal involvement in Rolandic brain regions, if present [12]. Genetic testing of the five most common genes mutated in YoAS is routinely offered to patients with a family history of YoAS (C9orf72, SOD1, TDP-43, FUS, TBK-1). Although there is no agreement on genetic testing for patients with sYoAS, there is a tendency to offer it to all patients [11]. However, genetic testing should only be performed if genetic counseling can be provided if a pathogenic gene mutation is identified. Gene panels containing rare genes associated with YoAS are emerging, but the diagnostic performance of the five most commonly mutated genes remains low.

Prognosis. Life expectancy in YoAS is highly variable. Many different clinical features present before the first manifestation of the disease are known to be associated with reduced survival. They include bulbar onset, short diagnostic delay, rapid functional decline [eg. as measured by the Revised YoAS Functional Rating Scale (ALSFRS-R)], significant weight loss (or body mass index), presence of frontotemporal impairment, older age at onset of symptoms, and lower life expectancy. In addition, genetic factors also affect life expectancy. Some monogenetic causes are associated with shorter survival (Ala5Val mutation in SOD1, C9orf72 repeat expansion, P525L mutation in FUS), but common and rare variants affecting survival have also been described. For example, homozygosity for the C allele of rs12608932 in UNC13a is associated with shorter survival [8]. The first individualized prediction models were developed that could estimate the survival outcomes of individual patients based on a combination of clinical parameters [7]. Such tools are valuable for patient selection or stratification in clinical trials and may be important for individualized risk assessment and care planning.

Conclusion: early detection of genetic biomarkers (SOD1, TARDBP, TBK1, FUS, PFN1, DCTN1, MuSK) in patients with YoAS can be the basis for thinking about the prognosis of the disease and implementing treatment measures earlier.

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