The Role of Collagen in the Pathogenesis, Pathophysiology and Treatment of Amyotrophic Lateral Sclerosis

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that affects the upper and lower motor neurons and is characterized by progressive paralysis and death from respiratory failure. The genetic heterogeneity of ALS is an obstacle to its diagnosis and treatment. For many years, the only orthodontic treatment for the disease was riluzole. In recent years, a second nosocomial treatment, entaravone, has been approved and used. In the present review, attention is focused on the levels of different collagen classes in patients with ALS. The role of certain forms of collagen that aim at both the pathogenesis and pathophysiology of ALS and in the treatment is presented. The specific characteristics of collagen that may concern us in the future are mentioned, either as biomarkers for the understanding and early diagnosis of the disease, or for new therapeutic approaches.

Key Words: Amyotrophic lateral Sclerosis, Treatment, Collagen

Introduction

Amyotrophic Lateral Sclerosis (ALS) is referred to as "Lou Gehrig's Disease", in honor of the baseball player who was diagnosed with ALS in 1939 and died in 1941, at the rage of 38. It is characterized by progressive paralysis and death from respiratory failure. Although the disease may affect at an early stage only the lower or only the upper motor neuron, in the long run it seems that both are involved. ALS, in most cases (90%) has a sporadic form (sALS), less often (10%) a positive family history is found in patients and is called familial cases (fALS). Epidemiologically, it is estimated that the disease ranges from 1 to 2 new cases per 100,000, per year, while its prevalence is 4 to 6 per 100,000 people. It affects men more often than women and is expressed in the adult phase of life. Life expectancy is quite unstable as it depends on the elation of ALS, however it is defined as 2-3 years from the onset of symptoms. The rate of progression of the disease may be faster in older people. The purpose of this review is the presentation of the data so far, the role of collagen in ALS, both for the prognosis of the disease and for its treatment. A thorough literature search was performed in the PubMed database using

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the key words ''role of collagen in ALS'' and ''role of collagen in neurodegeneration''.

Discussion

The search yielded 83 results in total, which 39 were excluded since they weren't relevant to this review. The full text articles of the remaining 44 records were then investigated for eligibility and 11 of those were excluded for various reasons, leaving 11 articles for the synthesis of this review. Finally, 5 articles were included which were identified from the literature of other researches (Figure 1).

Pathogenesis & Pathophysiology of ALS

Early diagnosis is an important role for the control and possible treatment of the disease, but the complexity of the mechanisms of action and the ambiguity of the symptoms has not allowed the existence of effective diagnostic tests to date. Often, patients experience muscle weakness, contractions and cramps resulting in problems in the muscles. At a more advanced stage they may experience more serious problems such as shortness of breath and dysphagia. The classification categories of ALS include: (a) Progressive Muscle Atrophy (PMA), (b) Progressive muscle paralysis (PBP), (c) Primary Lateral Sclerosis (PLS) and (d) Pseudopromic palsy. More than 50% of cases have cognitive function problems, while more than 13% are associated with frontotemporal dementia. As far as diagnostic criteria are concerned, the World Federation of Neurology, announced for the first time, in 1994, the so-called El Escorial, criteria that were revised and upgraded in 2000, taking the name Airle House. We arrive at 2008, where a new addition is made, the Awaji electrophysiological criteria, with the aim of diagnosing ALS at as early a stage as possible. The pathogenesis of ALS is not entirely clear, it remains unknown. There are several possible mechanisms associated with neurodegeneration, characteristic of the disease. ALS can be inherited in an autosomal dominant way, recessive or sex-linked. The main genes associated with the onset of ALS include: (a) superoxide Dismutase (SOD1), a cytoplasmic protein that breaks down peroxide roots and is involved in oxidative phosphorylation (3). Mutations in the SOD1 gene have been identified in about 20% of the familial and in about 1–4% of sporadic ALS cases (6). Localized mechanisms of action are incorrect folding and aggregation of proteins, oxidative stress, mitochondrial or axial dysfunction, a metabolic disorder through microglia as well as through cell apoptosis(7,8), (b) TARDBP and FUS are involved in the processing of RNA, reinforcing the hypothesis that disturbances in RNA metabolism can cause ALS. The first encodes the TDP-43 protein and has been identified at 0.7–2% in sporadic ALS and 4–6% in familial ALS cases, while the FUS gene encodes the sarcoma fusion protein and has been identified in 4% of familial and 1% of sporadic cases(3), (c) C9orf72, which is involved in the processes of intracellosis and autophagy(3,6). It has been identified by 40% in family cases and about 7% in the sporadic form of ALS.

To date, no effective treatment has been found, however, techniques are applied to slow the progression of the disease. For several years, riluzole extended survivorship in patients with ALS, mainly with pseudoprometic form of ALS. The pathophysiological mechanism is not fully known. It is thought to presynaptically inhibit the release of glutamic acid and increase its reuptake from the presynaptic endings. It acts as an indirect antagonist of glutamic acid and prevents its metasynaptic action, possibly interacting with the taseo-dependent sodium channels, stabilizing them in inactive form or with G-proteins. In this way it protects against overstimulation toxicity. Each patient follows various tactics and methods of slowing down symptoms, such as respiratory support that includes tracheostomy and non-invasive support, muscle relaxant treatment, physiotherapy exercises, use of gastrostomy in patients with dysphagia and administration of analgesic drugs. In 2017, the FDA approved entaravone (edaravone), a neuroprotective drug acting on CNS, as an antioxidant. Its mechanism of action remains unknown, however it seems to neutralize the free radicals of peroxide and hydroxyl in motor neurons. Other treatment options are still under study, including the chemical compound NU-9, stem cells as well as the effect of collagen.

Role of collagen

The most abundant fibrous proteins that are widespread in the extracellular space of all vertebrate tissues and

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other organisms are members of the collagen family. Collagen is the most abundant protein of our body. It provides the necessary structural integrity to the tissues, while regulating a variety of physiological functions. To date, approximately 28 genetically different types of collagen have been identified in vertebrates with various structural and biochemical characteristics. It is the main fibrous component of the skin, tendons, bones, cartilage, vessels and teeth. Its role in the organization is basically structural. It gives strength and maintains the integrity of the structure of connective tissue and organs of the body. It is found within the connective tissue not as an isolated molecule, but as a component of the complex system of tissue, which includes various other macromolecules such as elastin, glycoproteins and glycolipids. It serves to hold cells in distinct functional cell groups. Based on the function and homology of their sequence, several categories of collagen can be distinguished: (a) fibrin (types I, II, III, V, XI, XXIV and XXVII), (b) those forming networks (types IV, VIII and X), (c) those that form adhesion microfiberides (type VI), (d) those attached to fibrils with intermittent triple helix, known as FACIT (types IX, XII, XIV, XVI and XIX), (e) those characterized by multiple helical segments and interruptions and are called multiplexins (XV and XVIII). The role of collagen is not limited only to the maintenance of the structural integrity of tissues and organs. As a component of the basic membranes it acts as a molecular filter of substances. The interaction of collagen with agents, such as integrins, glycoproteins or specialized proteoglycan receptors, determines the differentiation, growth, adhesion, as well as the survival of cells. It binds growth factors and cytokines, as a result of which it plays a role in the development of organs, wound healing and tissue repair. Noteworthy is its application as a biomaterial in tissue mechanics, which aims at the regeneration, repair and replacement of human tissues for the treatment of diseases. Collagen is used in the manufacture of porous scaffolding, a three-dimensional construction that provides the necessary support for cells to attach, multiply and maintain their function. Its physical characteristics, combined with its biocompatibility and low immunogenicity, make it an excellent biomaterial. Its polypeptide skeleton contains many functional groups, facilitating access to genes, growth factors and other biological molecules. The type of collagen that is most used in tissue engineering is the one that is most abundant in the human body and has been studied the most, it is type I collagen. It is the most commonly occurring type in the upper vertebrates since about 80% of the collagen in the body consists of types I, II and III. It constitutes 90-95 % of the organic mass of bone and tendon and is the main type of collagen tissues, such as the skin, cornea, joints, dentin and arteries. Most connective tissues also contain this type of collagen, in addition to the vitreous cartilage, the brain and the vitreous fluid of the eye. Type I collagen is mainly composed in a large percentage of fibroblasts, osteoblasts and odontoblasts and in a smaller percentage some other types of cells present in tissues. The main role of type I collagen is structural, while it plays an important role in the proper development of tissues and organs. The collagen fibers of type I determine the shape and mechanical properties of the tissues, giving them the necessary stiffness and tensile potential. It contributes to the necessary hardness and endurance of the bone. The characteristic structure of the fibers of type I collagen is also important for the tendons that connect the muscles with the bones, as it offers them the possibility of more complex movements. It is involved in the healing process of wounds and fractures, and the processes that inhibit the synthesis of collagen delay their healing. Mutations in the genes encoding the triple helix chains of type I collagen or the proteins involved in the modifications of collagen during its biosynthesis can lead to various diseases. Collagen types I and III appear in a high concentration on the skin. It seems that collagen fibril diameter has a decreasing trend in ALS patients, is related to the pathogenesis of the disease but also has a direct relationship with the involvement of motor neurons. This degeneration is proportional to the length of time patients have been suffering. The fragmented and widely separated bundles of collagen in the tissue surrounding the capillaries and the markedly reduced amount of collagen in the posterior and anterior horn may be associated with the degeneration of upper and lower motor neurons in the spinal cord in ALS. The review, in addition, analyses the role of types IV, V, VI and XV, in the Peripheral Nervous System (PNS)

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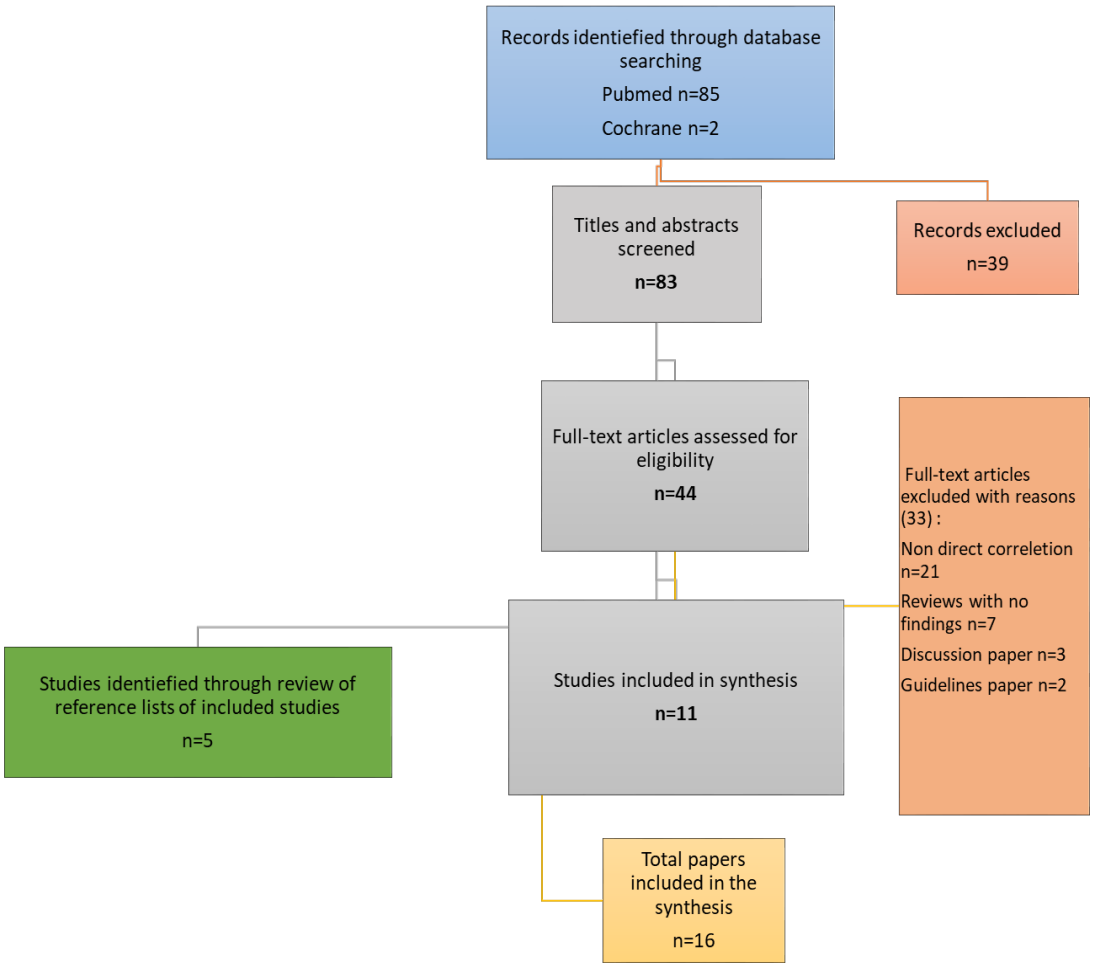
Figure 1.

Flow diagram showcasing the results of a search in the PubMed database and the selection process for the articles used in this review



in ALS patients. Collagen depletion brings changes in myelin levels and Schwann cells. Degradation of myelin makes it more difficult to transport impulses and thus either upper or lower motor neurons are affected. Of course, such information helps us to compensate for the appropriate types of collagen for functional nerve repair in people with ALS. Collagen VI is a peculiar component of the collagen superfamily made of 3 genetically distinct chains and abundantly deposited in the basement membrane of a variety of tissues, such as skeletal muscles skin, and peripheral nerves. It contributes to the structural integrity and physiological functions of peripheral nerve. Collagen VI regulates myelin thickness by modulating myelination-related signaling pathways. A proper thickness of myelin is required for the correct transmission of electrical impulses along the axons and preservation of axonal integrity in PNS. It is considered as a cell pro-survival factor, since collagen VI deficiency induces muscle cell apoptosis and enhances neuron death on toxic

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treatments in CNS.

Role of Collagen XIX

Finally, interest is turning to type XIX collagen, and this is because its levels are now typically elevated in ALS patients. This allows a more robust prognosis, especially in people who have shown the first symptoms. It has already become clear that there is a close relationship between ALS and COL19A1, which is now a predictive biomarker of the disease. Studies are being conducted on the role of type XIX collagen in terms of its importance in motor neuron degeneration for any disease in this category. Type XIX collagen is a building block of the basement membrane, a specialized extracellular matrix in vertebrates and some invertebrates. These membranes are present in the epithelium, connective tissue, blood vessel walls, axons, adipocytes, and muscle tissue. In addition, they present a dual functionality: on the one hand, these membranes maintain the tissue architecture, and on the other hand, they can regulate biological functions in contact with other cells by means of adaptive proteins. In this sense, they will play a task in cell migration, adhesion, differentiation, proliferation and taxis (Oudart et al., 2017). Although type XIX collagen was first identified in rhabdomyosarcoma cDNA clones, immunohistochemical analysis provided a wider distribution of this collagen in different human and muscle tissues, such as breast, colon, kidney, liver, placenta, cerebellum, prostate, cortex and hippocampus), skin and spleen (Sumiyoshi et al., 2001; Myers et al., 2003; Su et al., 2010; Oudart et al., 2017). Despite, the transcription and protein levels of type XIX Collagen (COL19A1) not only varies from embryonic to adult in some tissues, but also gradually decreases after birth, except in the brain where Col19a1 gene expression is ten times larger in adult mice than in embryonic mice condition (Sumiyoshi et al., 1997). Since its discovery in 1992, type XIX collagen has attracted attention among members of the FACIT family. To date, 42 genes encoding 46 different α chains have been identified in this collagen superfamily, which represents about 30% of the total protein weight in mammals and is also present in all invertebrate plants. (Brown and Timpl, 1995; Oudart et al., 2017).All of these family members share a triple helix consisting of three polypeptide segments aligned in parallel and their exclusive localization in extracellular matrices (Brown and Timpl, 1995). The main fact is that most of the α chains can contain several non-triple helical protein units, which gives more unit diversity than any other family of proteins as they are unique to this family or can be shared by other extracellular proteins (Brown and Timpl, 1995). These collagens are involved in the integrity and stability of the extracellular matrix, regulating the formation and size of collagen fibers and controlling cellular organization in the extracellular matrix (Oudart et al., 2017). Their specific localization in certain tissues and the fine-tuning of their expression make the members of the FACIT family key targets for understanding functional alterations in different cells and organs. In fact, type XIX collagen was discovered by a human rhabdomyosarcoma cell line (CCL-36) (Brown and Timpl, 1995; Oudart et al., 2017). The exact functions of this collagen are still unclear, although it is known to be involved in the formation and maintenance of the extracellular matrix, especially during the embryonic stage. In contrast, the biochemical characterization and chromosomal location of type XIX collagen have been analyzed in depth.

Conclusion

ALS is a rare and neurodegenerative disease, during which degeneration and death of motor neurons takes place step by step (Calvo et al., 2014; Al-Chalabi et al., 2016). In accordance with the Awaji criteria, each the higher motor neurons and therefore the lower motor neurons degenerate or die in ALS, and as a consequence communication between vegetative cell and muscle is lost, prompting progressive muscle weakening and therefore the look of fasciculations. From a diagnostic purpose of read, the analysis of the primary steps of ALS identification is troublesome since there's a large vary of neuron diseases that share its common and heterogeneous symptoms (Burgunder et al., 2011). Concerning ALS, the dysfunction and loss of each higher and lower motor-neurons beside gradual jerkiness could also be gift within the weakened limb, poignant sleight and gait though there ought to be no involuntary, sensory, or psychological feature involvement (Vucic and Kiernan, 2009). Therefore, the necessity of distinguishing reliable diagnostic or

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prognostic biomarkers in ALS is AN increasing field of analysis. This study was designed and performed to spot the role of scleroprotein for ALS malady progression that might be in shut reference to the clinical parameters for a much better observance and stratification of the patients. The start line during this study was the muscle tissue though we tend to additionally explored blood tissue to spot and validate prognostic biomarkers in an exceedingly non-invasive manner. High levels of COL19A1 might act as a countervailing response once the malady progression is quick, that is in accordance with previous studies that urged a detailed relationship between COL19A1 factor and ALS in muscle biopsies from ALS patients. These findings unconcealed the potential use of COL19A1 to boost prognosis within the malady progression in an exceedingly non-invasive manner. the mixture of high COL19A1 expression levels and a quicker malady progression will promote a shorter life in ALS patients, and so COL19A1 levels may be thought of a reliable blood-derived biomarker in muscle biopsies and in blood to support the clinical apply and to be of facilitate in future clinical trials, further as a promising and novel therapeutic target in ALS.

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