Tuzim Kamila, Tuzim Tomasz, Urbańczuk Magdalena, Urbańczuk Marcin, Schab Katarzyna. **Amyotrophic lateral sclerosis – aetiology, diagnostics and multidirectional, team, long-term care. Journal of Education, Health and Sport. 2018;8(8):650-657. eISNN 2391-8306. DOI** http://dx.doi.org/10.5281/zenodo.1343951
http://ojs.ukw.edu.pl/index.php/johs/article/view/5793

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.08.2018. Revised: 03.08.2018. Accepted: 11.08.2018.

Amyotrophic lateral sclerosis – aetiology, diagnostics and multidirectional, team, long-term care

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ABSTRACT

Amyotrophic lateral sclerosis *(ALS)* is a rare neurodegenerative disease of brain motoneurons and spinal cord. The incidence rate of this completely incurable condition amounts to 3 to 5 patients per 100,000 inhabitants and its characteristic feature is progressing muscle weakening that leads to respiratory muscle paralysis and death within 3-4 years. Up to now, etiopathogenesis of *ALS* is unknown, however, more and more often the role of genotype interaction with environmental factors is suggested. Diagnosing *ALS* is still based on a correlation of interview and clinical picture with the results of diagnostic imaging, electrophysiological examinations and some serological tests. Despite an enormous progress that occurred in neurobiology and molecular genetics, an effective pharmacotherapy inhibiting the development of the disease has not been developed yet, and the treatment is exclusively based on a systematic symptomatic management. Due to the above, *ALS* treatment is still a great challenge both for the scientists and clinicians.

Key words: amyotrophic lateral sclerosis, *ALS*, electrophysiological examination, riluzole, edaravone, replacement ventilation.

INTRODUCTION

Amyotrophic lateral sclerosis *(latin: sclerosis lateralis amyotrophica, ALS, SLA*) is a heterogeneous, progressive neurodegenerative disease of unknown aetiology and pathogenesis, which damages both the upper motor neuron *(UMN)* and the lower motor neuron *(LMN)*. This condition has been known for more than 130 years – in 1869 a French physician Jean-Martin Charcot described its symptoms for the first time [1]. In 1941 *ALS* became infamously renowned in the USA when it caused the death of one of the most outstanding American athletes – a baseball player Henry Louis (Lou) Gehrig known as the Iron Horse – so this condition is also known as "Lou Gehrig's disease". In the USA and Europe *ALS* occurs with a frequency of 1 to 2 new cases per 100,000 people. In the general population the incidence oscillates around the level of 3 to 5 per 100,000 [2]. As lifetime risk of developing *ALS* amounts to approximately 1:350 for men and 1:400 for women, it is estimated that only in the USA 800,000 of currently alive people will die of the above-mentioned disease [3]. An increase in the incidence rate of *ALS* has not been observed in the recent years. Ninety percent of cases are sporadic form of the disease *(SALS)*, that is characterised by a predilection to male gender (male to female rate ratio – 2:1). The number of female and male patients with *ALS* becomes equal after 70 years of age. Lower incidence of the disease in women is explained by a possible protective action of female sex hormones that may be confirmed by the increasing incidence among older women [4]. The remaining 10% are gender-independent familial form of the disease *(FALS)*, whose development is influenced by more than 30 various genes. *FALS* is usually autosomally dominantly inherited, with high mutation penetration. Autosomal recessive inheritance is sporadically observed [5-7]. As a disease typical for the middle age, *SALS* usually begins at the end of the 50th year of life, with peak incidence at 65 years of life; the average time since the occurrence of the first symptoms of the disease to the diagnosis is approximately 12 months. In 20% of cases *ALS* develops after the 70th year of life suggesting that it is also a neurodegenerative disease of advanced age. Despite the fact that the mean survival rates are very diverse, usually respiratory disorders lead to death within 3-4 years since the diagnosis [1,7,8]. Appearance of the first symptoms in late puberty period or in the early adulthood suggests genetic determination of the disease. In case of *FALS* the disease usually appears a decade earlier and the mean survival is shorter than in *SALS* [5]. If the disease starts before the age of 25, a term juvenile *SLA (JALS)* is used [9].

AETIOLOGY AND PATHOMECHANISM OF *ALS*

Based on the results of clinical and control studies, several probable, environmental triggering factors of *ALS* were found. There are some premises that a neurotoxin β-methyl-amino-L-alanine *(BMAA)*, produced by cyanobacteria of Nostoc genus may participate in the pathogenesis of ALS. There is also an increasing evidence for the role of nicotinism, exposure to heavy metals (mainly manganese), pesticides and electromagnetic radiation in the induction of *ALS*. Among biological factors a role of human endogenous retrovirus K, *HERV-K*) is mentioned, whose presence has been already confirmed in cortical and spinal motor neurons of patients with *ALS*. What is interesting, intense physical activity is thought to increase the risk of disease development. On the contrary, type 2 diabetes mellitus, hyperlipidaemia and hormonal contraception probably exhibit a protective action. Moreover, presence of injuries, including head injuries, in the etiopathogenesis of *ALS* is suggested. Therefore, those who practice sport exposing them to repeated brain concussions, belong to a high-risk group [7,8,10].

Post-mortem macroscopic image is dominated by atrophy of skeletal muscles and motor cortex atrophy, fading and hardening of pyramidal ways, thinning of sublingual nerve and ventral roots of the spinal cord. In turn, microscopic preparations were characterised by more than 50% depletion of spinal motor neurons, diffuse astrocytic gliosis and microglial infiltration of white and grey matter of the spinal cord. The above histopathological lesions are an outcome of aggregation of ubiquitin protein insertions inside motor neurons that, in turn, is a result of numerous pathomechanisms. The most frequently mentioned ones are disturbance of protein homoeostasis, improper *RNA* metabolism, disturbance of vesicular, endosomal and nucleocytoplasmic transport, impairment of axonal structure and function, improper *DNA* repair mechanisms, excitotoxicity, oligonucleotide degeneration, neuroinfection and mitochondrial dysfunction [10].

Defects within the above-mentioned mechanisms are a secondary phenomenon to the genetic abnormalities. Genome-wide association study *(GWAS)* conducted in patients with supposed sporadic form of the disease suggested that a complex genetic architecture of *ALS* is based on rare allelic variants. However, this procedure is not dedicated to the analysis of genetic predisposition of the discussed condition, because rare variants that remain in association with the disease may be also specific for a single individual, family or lineage. Current knowledge on the genes responsible for the development of *ALS* is based on the results of studies involving a population of native Europeans and inhabitants of eastern Asia. Dichotomization of the disease in the above group of patients, to sporadic and familial subtype, seems to be an exaggerated simplification. Despite the fact that more than 30 genes have been identified whose mutation increases the risk of developing *ALS*, there are undeniable proofs postulating for the participation of oligogenic model of inheritance and gene pleiotropy in the pathogenesis of the disease. In 60-80% of cases of familial form of the disease, mutations in 1 of 4 from the following genes were detected: *C9orf72* (40%) coding protein *C9orf72*, *SOD1* (20%) coding superoxide dismutase, *FUS* (1-5%) coding nuclear RNA-binding protein and *TARDBP* (1-5%) coding nuclear protein *TDP43* [8].

SYMPTOMATOLOGY AND COURSE OF *ALS*

In 2/3 of patients a classical form of *ALS*, the so-called Charcot disease occurs. Its initial phase is characterised by asymmetrical, focal paresis and muscle atrophy in the upper or lower extremities. Sometimes the first symptom of the disease is spastic paraparesis of lower extremities. In rare cases prodromal symptoms in the form of fasciculations or muscle spasms are precursors of the disease, insidiously preceding the occurrence of proper symptoms of the disease by several months and even years. Fasciculations and atrophy of tongue muscles are almost pathognomonic symptoms of *ALS*. Paresis and muscle atrophies, intensifying under the influence of cold, undergo continuous progression diffusing locally (within the same body region, i.e. from hand to the deltoid part) or in the direction of the associated neuroanatomical regions (cranially, caudally or contralaterally). In the limb affected by the pathological process spasticity gradually occurs that in combination with paresis hinders manual activities. In the terminal stage of the disease flexion contractures appear that are induced by an increased activation of flexor reflex arc in the spastic limb. In a typical *ALS*, motor neurons of Edinger-Westphal nucleus and Onuf nucleus are not included in neurodegeneration, so the function of oculomotor muscles and sphincters is preserved [8]. Bulbar symptoms with further respiratory distress and pulmonary complications finalize the course of disease process [11].

In the advanced stage of *ALS*, in patients with tracheostomy and artificial ventilation, the so-called locked-in syndrome may occur as a result of general paresis of striated muscles, including the oculomotor muscles [12].

The main bulbar symptom in *ALS* is dysarthria, initially noticed after alcohol consumption, finally leading to complete anarthria within 6-12 months. Infrequently, it is preceded by dysphagia for solid or liquid food. Patients usually complain about salivation resulting from disturbed saliva swallowing and transitory, bilateral, supranuclear paresis of lower facial muscles. Parallelly to dysarthria, within 2 years, limb signs develop [11]. Almost half of the patients show pseudobulbar syndrome described as emotional lability and a tendency to inadequate reactions to emotional stimuli in the form of explosive cry or laughter [7]. In this form of the disease prognosis is worse and median survival amounts to 2 to 4 years since the moment of diagnosis [11].

Atypical onset of the disease, with respiratory distress and absence of limb signs and bulbar symptoms, concerns 5% of patients who often have been already diagnosed in cardiology or pulmonology departments before the proper diagnosis is made [13]. Then, a picture of the disease consists of: dysarthria preceding dysphagia, morning headaches, excessive somnolence during a day, sleeping disorders, decreased concentration, distinct irritability, mood changes, dyspnoea and unexplained body weight loss [11].

The other, rarely occurring ALS forms include progressive muscular atrophy *(PMA)*, its variants: flail arm (also known as Vulpian-Bernhardt syndrome) and flail leg (described as pseudopolyneuropathic variant, *FL*), or primary lateral sclerosis *(PLS)* [11].

Cognitive or behavioural disorders of various intensity quite often are an inseparable component of some forms of *ALS*. They can precede or follow the appearance of neurological deficits associated with motor neuron damage [14]. Clinical features of frontotemporal dementia *(FTD)* occur in 5-15% of patients, whereas more than 50% of patients reveal the behavioural and cognitive symptoms of *FTD* spectrum [15-18]. Dominant behavioural symptoms are: apathy and loss of compassion observed in approximately 10% of patients [19]. Cognitive profile of *ALS* is characterised by impaired fluency, language, social cognition and executive functions. In one group of patients memory disorders are observed, which are rarely isolated [20]. Early diagnosis of cognitive and behavioural disorders is extremely important due to their correlation with genetic mutations (i.e. *C9orf72*, *TBK1*), more aggressive course of the disease and, as a result, more heavy burden of caregivers [21,22].

DIAGNOSTICS OF ALS

Lack of a diagnostic test specific for *ALS* or a sensitive and specific enough biological biomarker leads to diagnosing the disease usually based on the interview, clinical picture, results of electrophysiological examinations, diagnostic imaging or laboratory tests. The above data are confronted with standard criteria of diagnosing *ALS* – El Escorial and Airlie House [23].

Electroneurography *(ENG)*, usually normal in *ALS*, serves for exclusion of diseases of peripheral nerves and neuromuscular junction, mainly polyneuropathy with conduction block, for which there is an effective treatment. In turn, electromyography *(EMG)* results provide undeniable evidence for the involvement of *LMN*. It is necessary to perform *EMG*

examination for many muscles innervated by different spinal cord segments, i.e. Cervical segment, thoracic segment, lumbar segment and the bulb. For electrophysiological diagnosis of *ALS*, it is necessary to detect denervation and reinnervation features in 2 out of 4 of the above-mentioned regions of the central nervous system. There are also several other methods of estimation of a number of active motor neurons based on clinical neurophysiology – the so-called *MUNE* (motor unit number estimation) examination. Transcranial magnetic stimulation *(TMS)* is used for the assessment of corticospinal tract damage [11].

Degeneration of corticospinal tracts is responsible for hyperintense lesions within their course in brain and brainstem, rarely in the spinal cord, observed in *T2* and *FLAIR* images in magnetic resonance imaging *(MRI)* [24].

During the pathogenesis of *ALS* neurofilament degradation occurs. Thus, both in serum and in the cerebrospinal fluid an increased concentration of neurofilament light chain *(Nf-L)* and phosphorylated neurofilament heavy chain *(pNf-H)* is observed [8]. Creatine phosphokinase *(CPK)* activity usually does not exceed the 10-fold of the upper limit of the normal range [11].

In skeletal muscle biopsy, not required for the diagnosis, various, mainly non-specific lesions were described. Microscopic images revealed the presence of scattered hypertrophic fibres accompanied by moderate clustering of fibres at the presence of a scarce number of fibres undergoing necrosis [11].

ALS THERAPY

Up to now, results of numerous clinical trials conducted all over the world did not lead to the development of an effective medication inhibiting the course of *ALS*. Thus, treatment of the symptom is based on multidirectional cooperation of neurologists, psychologists, speech therapists, occupational therapists, physiotherapists, dietitians, gastroenterologists, pulmonologists, general practitioners or social workers and its main aim is to optimize both pharmacological and non-pharmacological management. Multidisciplinary approach prolongs mean survival time, thus improving the quality of life *(QOL)*, reduces the number of hospital admissions and shortens mean hospitalisation time [10].

During the analysis of more than 50 various chemical substances with different mechanisms of action, only 2 were selected– riluzole (2-Amino-6-(trifluoromethoxy)benzothiazole) and edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) – that slightly prolong the mean survival time of patients with *ALS*. The first medication accepted by the Food and Drug Administration Agency (*FDA)*, riluzole, inhibits glutamatergic transmission by blocking voltage-dependent sodium channels in presynaptic neurons. According to the metaanalysis by Cochrane Library, its daily administration at the dose of 100 mg for 18 months slightly prolongs the mean survival from 11.8 to 14.8 months compared to placebo, however it does not have the effect on the improvement of muscular strength [25,26]. Riluzole has a relatively safe safety profile and its most common adverse effects include elevation of liver enzyme concentration and asthenia. Despite the fact that it extremely rarely leads to acute pancreatitis and liver damage, taking this medication requires monthly monitoring of complete blood count and transaminase levels. In case of a three-fold excess of liver enzyme normal range or neutropoenia, the medication must be withdrawn immediately [10,11]. Edaravone, approved by *FDA* but not approved by the European Medicines Agency *(EMEA)* as an oxidative stress suppressor, inhibits *ALS* progression in a strictly selected population of patients with early-onset form of the disease and its rapid course [27,28].

ALS is an uncurable disease, but many of its consequences may be prevented or alleviated always taking into account the improvement of patient's quality of life and complete respect of his autonomy.

Spasticity is noted in the majority of patients, but few of them require pharmacotherapy, usually with the use of baclofen, tizanidine or, more rarely, cannabinoids (off-label use).

An implication of hypersalivation, one of the most frequent ailments in bulbar onset form of the disease or in the terminal stage of the disease, is the use of anticholinergic drugs, i.e. atropine and hyoscine, amitriptyline, glycopyrrolate and in case of ineffective pharmacotherapy – intrasalivary injections of A and B botulinum toxin or radiation of salivary glands.

Pain treatment in *ALS* is also an important challenge requiring a comprehensive approach including medications together with physiotherapy. Gabapentin, pregabalin and tricyclic antidepressant drugs bring relief in a more rarely occurring neuropathic pain. In turn, in case of a definitely more frequent nociceptive pain it is worth taking nonsteroidal anti-inflammatory drugs, opioids or intra-articular injections of lidocaine or steroids. The main cause of pain are unpleasant muscle contractions resulting from instability of motor units, which are present in ¼ of patients with spinal-onset ALS. The above-mentioned symptoms are effectively alleviated by quinine sulphate, levetiracetam and mexiletine [10].

Dysphagia is another frequent and potentially dangerous symptom developing within 2 years since the appearance of the first *ALS* symptoms in 60% patients with spinal subtype of the disease and in all the patients with the bulbar subtype. This symptom may result in choking, malnutrition, dehydration and body mass loss [29]. Basic management of dysphagia, aiming at the reduction of its complications, includes the introduction of a properly balanced, high-protein and high-calorie diet, enriched with thickeners for liquid food products. A compensatory action consisting in the introduction of a new swallowing technique (the so-called supraglottic swallowing with the appropriate head position and its bent forward) that improves its effectiveness and safety is important as well. Body mass loss of more than 10% is an indication for introducing an alternative way of food administration, i.e. percutaneous endoscopic gastrostomy *(*PEG*)* and nasogastric tube (*NGT)* [11,30].

A determinant of communication disorders in patients with *ALS* is dysarthria sometimes even leading to complete anarthria. Speech therapy is the main objective in speech disorders.

Prolonged stay in seated position and restricted mobility of patients with *ALS* promote the development of deep vein thrombosis. Due to the above, it is advised not to forget about compression therapy and anticoagulation in symptomatic management [11].

Cognitive disorders and mood disorders, in 50% in the form of depression, indicate the need of using selective serotonin reuptake inhibitors *(*SSRI) and tricyclic antidepressant drugs [10].

The main cause of mortality in the discussed group of patients is respiratory distress. Initially, non-invasive ventilation (Non-invasive ventilation, *NIV*) is used that mainly includes bilevel positive airway pressure *(BiPAP)* and rarer continuous positive pressure ventilation *(CPAP)* [31]. It prolongs the mean survival time (by 7 months) and improves the quality of life more

effectively compared to riluzole [32]. In order to maximize the effectiveness of cough, a cough assist machine, mechanical insufflator-exsufflator, is used [33]. Using antibiotic therapy is also indicated during each respiratory tract infection, as well as flu vaccination every year. In the final stage of the disease, when *NIV* is not able to compensate for respiratory disturbances, invasive ventilation after the tracheostomy formation is performed, respecting patient's right to decide about himself or herself.

CURRENT DIRECTIONS IN THE THERAOHY IN *ALS*

The main directions of development of *ALS* treatment strategies are currently based on mitochondrial protection (dexpramipexole, rasagiline), immunomodulation (fingolimod, *CDP7657, NP001,* tocilizumab), autophagy stimulation (lithium carbonate), inhibition of the appropriate kinases (masitinib, fasudil hydrochloride, *GSK2606414* and kenpaullone), gene therapy (*anti-SOD1* antibody and antisense oligonucleotides) and cell therapy (astrocyte replacement, neural stem cell therapy and immunosuppressants) [34].

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