Plasma levels of soluble RAGE, AGEs and AOPPs at the early stage of amyotrophic lateral sclerosis: A preliminary study

Stężenie rozpuszczalnego RAGE, AGE i AOPP w osoczu we wczesnym stadium stwardnienia zanikowego bocznego – badania wstępne

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Abstract

Background. Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder with largely unknown pathogenesis and no effective cure. It is believed that several, not mutually exclusive mechanisms contribute to the pathogenesis and progression of this disease, including, among others, elevated oxidative stress, excitotoxicity, increased neuroinflammation, and protein aggregation. Receptor for advanced glycation end products (RAGE) is a part of immunoglobulin superfamily; it is believed to participate in ALS pathogenesis.

Objectives. Our previous studies on ALS demonstrated that RAGE is likely one of the key players in ALS, acting on its own and in tandem with its oxidative stress and pro-inflammatory ligands, such as advanced glycation end products (AGEs) or advanced oxidation protein products (AOPPs). In this study, based on our previous results, we aimed to establish blood levels of soluble RAGE, AGE and AOPP in ALS patients.

Materials and methods. Forty-six coded and anonymized surplus plasma samples from ALS patients and non-neurological control were used in the study. The plasma levels of RAGE, AGE and AOPP were measured using enzyme-linked immunosorbent assay (ELISA) commercially available kits. Statistical evaluation of data was performed using one-way non-parametric analysis of variance (ANOVA) with Kruskal–Wallis post hoc test.

Results. Our results revealed a decline in soluble RAGE level, concurrent with an increase in the levels of AGEs and AOPPs in blood samples from ALS patients, signifying a loss of neuroprotective form of RAGE and a simultaneous increase in AGE and AOPP production and uptake at the early stage of the disease.

Conclusions. The results obtained from our study indicate that further longitudinal study of RAGE, AGE and AOPP levels would be beneficial, outlining the dynamics between RAGE and its ligand levels as the disease progresses, and making them valuable diagnostic tools and potential therapeutic targets.

Key words: receptor for advanced glycation end-products, advanced glycation end-products, advanced oxidation protein products, amyotrophic lateral sclerosis, plasma

Streszczenie

Wprowadzenie. Stwardnienie zanikowe boczne (amyotrophic lateral sclerosis (ALS)) jest wyniszczającą chorobą neurodegeneracyjną o nieznanej patogenezie i bez skutecznego leczenia. Uważa się, że w patogenezie i postępie tej choroby bierze udział kilka niewykluczających się wzajemnie mechanizmów. Należą do nich m.in. podwyższony stres oksydacyjny, ekscytotoksyczność, okołonerwowe odczyny zapalne i agregacja białek. Receptor końcowych produktów zaawansowanej glikacji (RAGE) należy do nadrodziny immunoglobulin i uważa się, że bierze on udział w patogenezie ALS.

Cel pracy. Nasze wcześniejsze badania ALS wykazały, że RAGE jest prawdopodobnie jednym z kluczowych graczy w tej chorobie, działając samodzielnie bądź w połączeniu z ligandami stresu oksydacyjnego i zapalenia, takimi jak zaawansowane produkty końcowe glikacji (AGE) lub zaawansowane produkty utleniania białek (AOPP). W niniejszej pracy, w oparciu o nasze poprzednie wyniki, mieliśmy na celu ustalenie stężenia rozpuszczalnego RAGE, AGE i AOPP w próbkach krwi pochodzących od pacjentów z ALS.

Materiał i metody. W badaniu wykorzystano 46 zakodowanych i anonimowych próbek krwi pochodzących od pacjentów z ALS i grupy kontrolnej. Badanie zostało zaprojektowane zgodnie z założeniami Deklaracji Helsińskiej i zatwierdzone przez Instytucjonalną Komisję Etyki. Poziomy RAGE, AGE i AOPP w osoczu mierzono za pomocą dostępnych komercyjnie zestawów ELISA. Statystyczną ocenę danych przeprowadzono za pomocą jednokierunkowej nieparametrycznej ANOVA z post-testem Kruskala–Wallisa.

Wyniki. Uzyskane wyniki wykazały spadek stężenia rozpuszczalnego RAGE przy jednoczesnym wzroście stężenie AGE i AOPP w próbkach krwi od pacjentów z ALS, wskazując na utratę neuroprotekcyjnej formy RAGE i jednoczesne nasilenie produkcji oraz wychwytu AGE i AOPP we wczesnym stadium choroby.

Wnioski. Wyniki uzyskane w naszym doświadczeniu wskazują, że dalsze długotrwałe badania stężenia RAGE, AGE i AOPP byłyby korzystne, umożliwiając określenie dynamiki zmian między stężeniem RAGE i jego ligandów w miarę postępu choroby, i tym samym dostarczając cennych narzędzi diagnostycznych i potencjalnych celów terapeutycznych.

Słowa kluczowe: receptor końcowych produktów zaawansowanej glikacji, końcowe produkty zaawansowanej glikacji, zaawansowane produkty utleniania białek, stwardnienie zanikowe boczne, osocze

Background

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal motor neuron disease first described in 1869. Since its discovery, it has been associated with progressive motor neuron death, muscle weakness, loss of motor functions, disability, and death within few years after the initial diagnosis.[1] It is an adult-onset disease with an incidence of 1–5/100,000 in most population, with a predicted 69% increase in its cases over the next 25 years. Clinically, depending on the onset of first clinically observed symptoms, ALS is divided into 2 forms: spinal (affecting limb muscles) and bulbar (impacting head and neck muscles). Of those, spinal form is far more prevalent, diagnosed in about 70% of ALS cases.[2]

It is believed that several, not mutually exclusive, mechanisms contribute to pathogenesis and progression of this disease. These include elevated oxidative stress, excitotoxicity, increased neuroinflammation, mitochondrial dysfunction, disruption of the neurofilament network, protein aggregation, cytoskeletal dysfunction, and involvement of non-neuronal cells within motor neuron surroundings.[3–7]

The receptor for advanced glycation end products (RAGE) is a part of immunoglobulin superfamily and belongs to the group of pattern recognition receptors involved in pathogen- or damage-associate molecular pathways (PAMP and DAMP, respectively).

Physiologically, RAGE is largely present on the surface of endotheliocytes, neural and immunocompetent cells, e.g., neurons, glia, lymphocytes, and macrophages, respectively.[8] Receptor for advanced glycation end products, aside from binding to advanced glycation end products (AGEs), interacts with over 25 different molecules, including advanced oxidation protein products (AOPPs), S100/calgranulin, HMGB1/amphoterin, amyloid-beta peptide (Aβ), transforming protein RhoA, protein diaphanous homolog 1 (Diaph1), and many others.[8] The engagement of RAGE by AGEs or its other ligands in a variety of settings initiates prompt generation of reactive oxygen species (ROS), upregulation of inflammatory pathways, and other RAGE signaling-dependent mechanisms. Receptor for advanced glycation end products is well known to be involved in the progression and pathogenesis of several neurodegenerative diseases and conditions.[9,10] Although the detailed mechanisms of RAGE involvement to the neurodegeneration remains unclear, studies indicate that it exerts its detrimental actions via its binding to the pro-inflammatory ligands such as AGEs, S100/calgranulin and amphoterin, and subsequent activation of downstream regulatory pathways such as NF-κB, STAT and JNK signaling. Soluble RAGE is a truncated form of RAGE, acting as a decoy for a full-length RAGE. Studies have implicated that soluble RAGE counters the detrimental action of a full-length RAGE, making it a promising therapeutic target in ALS treatment.[11] Our previous studies demonstrated that RAGE deficiency improves post injury sciatic nerve regeneration

in type 1 diabetic mice, at least in part by reducing tissue-damaging inflammation at the injury site.[12] We also showed that in SOD1 93A mice, a common animal model of ALS, daily administration of soluble RAGE delays the onset and prolongs the lifespan of ALS mice, further underscoring its potential in ALS therapy. The results of our earlier studies with human and murine ALS-affected spinal cords revealed an overexpression of RAGE and its ligands in motor neurons, microglia and astrocytes.[13,14]

Our most recent studies further underscored the importance of RAGE-signaling, uncovering that the conditional RAGE knockout in microglia cells in ALS spinal cord extends the lifespan of SOD1 93A mice.[15] We also revealed time-depended changes in the expression of RAGE and its ligands in ALS mice over the course of the disease.[16]

Based on our previous results and collective evidence on the role of RAGE in ALS mouse models, we aimed to determine the levels of soluble RAGE, AGE and AOPP in donated blood surplus of early-stage ALS patients admitted to the Department of Neurology of Jagiellonian University Medical College (Cracow, Poland).

Materials and methods

Blood samples

Forty-six donated, coded and anonymized surplus plasma samples of ALS patients aged 30–73 (median age 55): 14 women of average age 55.7 ±6.3 years and 32 men of average age 55 ±10 years, and 11 non-neurological controls, aged 31–47 (median age 36) treated at the regional hospital were used in the study. All ALS patients were evaluated using Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), scoring on average 46–48 points, and were classified as early-stage ALS. Samples were categorized according to the onset of the disease: spinal or bulbar. All patients met clinical and electrophysiological criteria of ALS as set in El Escorial criteria (EEC). Amyotrophic lateral sclerosis and control blood was donated and coded at the time of diagnosis. The study was designed in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Ethics Committee at the Jagiellonian University (approval No. 501/NKL/32/L).

RAGE, AGE and AOPP level measurement

The plasma levels of RAGE, AGE and AOPP were measured using enzyme-linked immunosorbent assay (ELISA) commercially available kits, i.e., Human RAGE Quantikine ELISA Kit (R&D Systems, Minneapolis, USA), OxiSelect™ AGE Competitive ELISA Kit and OxiSelect™ AOPP Assay Kit (Cell Biolabs Inc., San Diego, USA). Statistical evaluation of data was performed using one-way non-parametric analysis of variance (ANOVA) with Kruskal–Wallis post hoc test using GraphPad software (GraphPad Prism, San Diego, USA).

Results

Changes in the levels of various plasma proteins are often used as a diagnostic and/or prognostic tool in detecting a specific disease and assessing its progression. The clinical validity of plasma protein measurement has been established in routine testing for bone marrow disorders, liver and kidney diseases, leukemia, or cardiovascular disease (CVD).[17] However, the validity of using plasma markers in diagnosis and/or assessment of progression in neurodegenerative disease have been scarce and mainly limited to testing only for Alzheimer's disease (AD).[18,19] A number of studies offering insight into the use of plasma markers in ALS have been limited. Therefore, based on our previous research and research conducted by others, we attempt to fill in the gap by investigating the potential value of RAGE, AGE and AOPP plasma levels as prognostic markers of ALS.

RAGE

A significant reduction of soluble RAGE levels was detected in spinal and bulbar plasma samples as compared to the control (Fig. 1). This indicates the loss of neuroprotective, soluble form of RAGE already at the early stage of the disease. The mean values plus SEM were as follows: control – 720.5 ±81.66 pg/mL, spinal ALS – 365.2 ±43.66 pg/mL and bulbar ALS 257.7 ±96.46 pg/mL.

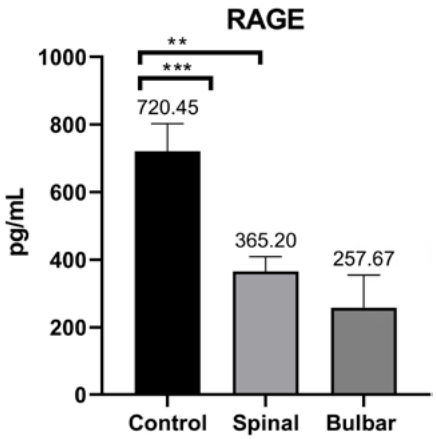

Fig. 1. Soluble plasma levels of receptor for advanced glycation end products (RAGE). The levels of soluble RAGE were significantly decreased in both groups of patients with ALS as compared to controls and, on average, the observed reduction was more noticeable, but not reaching statistical significance, in the bulbar group as compared to the spinal group; ** denotes $p < 0.01$ and *** denotes $p < 0.001$; bars represent standard error of the mean (SEM), mean value for each group is given above the corresponding bar

AGEs

An increasing trend in AGE plasma concentration was observed in spinal and bulbar plasma samples as compared to the control group (Fig. 2). This trend may reflect an uptake of pro-inflammatory AGE production already at the early stage of the disease. The mean values plus

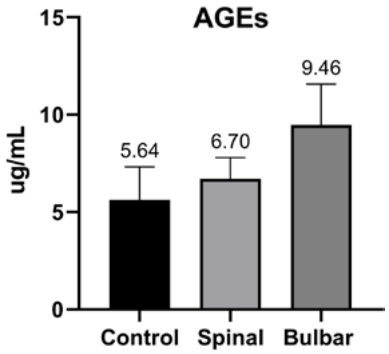

Fig. 2. Plasma levels of advanced glycation end product (AGE). While an increasing trend, signifying increased AGE activity, was noticed in both amyotrophic lateral sclerosis (ALS) groups, the increase was not yet statistically significant. The increasing trend more pronounced in plasma of the bulbar group was likely reflecting higher production of AGEs as compared to the spinal onset and to the control group; bars represent standard error of the mean (SEM), mean value for each group is given above the corresponding bar

SEM were as follows: control – 5.64 ±1.68 μg/mL, spinal ALS – 7.8 ±1.09 μg/mL and bulbar ALS 9.46 ±2.1 μg/mL.

AOPPs

Plasma analysis revealed high basal concentrations of AOPPs in all studied groups, on average 2.5 times higher as compared with the corresponding AGE levels. Similarly to AGEs, at the early stage of the disease, we observed an increasing trend in AOPP concentration in spinal and bulbar ALS as compared to controls (Fig. 3). The mean values plus SEM were as follows: control – 19.11 ±7.4 μmol/L, spinal ALS – 23.36 ±5.87 μmol/L and bulbar ALS 26.82 ±12.77 μmol/L.

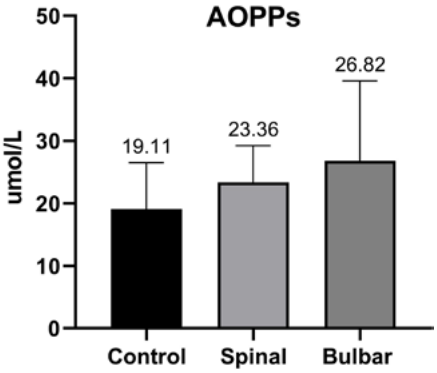

Fig. 3. Plasma levels of advanced oxidation protein products (AOPPs). Similarly to advanced glycation end products (AGEs), the levels of AOPPs were also increased in both amyotrophic lateral sclerosis (ALS) groups as compared to controls, with highest values observed in the bulbar groups. However, the observed increase was not statistically significant at this stage of the disease; bars represent standard error of the mean (SEM), mean value for each group is given above the corresponding bar

Discussion

Our present study focused on determining the plasma levels of soluble RAGE, AGE and AOPP at the early stage of ALS. We found that while the levels of soluble RAGE, a physiological antagonist of a full-length RAGE, were already significantly reduced, the levels of AGE and AOPP showed increased activity level compared to controls.

The results of our study are consistent with the study by Iłżecka,[20] who reported significantly reduced expression of soluble RAGE in ALS patients. Numerous studies show the correlation between the level of soluble RAGE on the onset and/or during progression of various neurodegenerative or metabolic diseases.[20–24] Reports from diabetes and atherosclerosis studies have revealed correlations between the levels of soluble RAGE and the severity of the pathological processes in a given disease.[25–27] Similarly, clinical reports from studies of neuroinflammatory disorders such as multiple sclerosis (MS) or Guillain–Barré syndrome have reported low levels of circulating soluble RAGE in both diseases compared to the controls, which correlated with the disease severity.[28–30]

However, in patients with MS who underwent CinnoVex (IFNβ-1a) or fingolimod (sphingosine-1-phosphate receptor modulator) treatments, the levels of soluble RAGE were increased, which corresponded to a positive treatment response, emphasizing the possible role of soluble RAGE in reducing neuroinflammation in affected tissue, thus diminishing the signs and symptoms of the disease.[31,32]

Despite the fact that studies on the use of soluble RAGE as a specific marker of ALS progression are still in the early stages, based on evidence derived from our and other recent translational studies demonstrating the involvement of RAGE in the pathogenesis of ALS, we might assume that measuring RAGE level, especially in conjunction with AGE and AOPP, could be a prognostic marker of ALS progression. Our study demonstrated that blocking RAGE signaling with soluble RAGE delays the progression of the disease and slows down the motor function decline. A recent study by Liu et al. supports our results, revealing that RAGE inhibition by soluble RAGE-like inhibitors, such as RAGE antagonist peptide (RAP) and FPS-ZM1, has a positive effect on motor neuron survival and reduced gliosis, effectively improving motor function in ALS mice, but not extending lifespan.[14,33]

Taken together, these results indicate that the role of RAGE in ALS progression might extend beyond secondary involvement, making it a potential marker and therapeutic target.

Opposing the observed reduction in plasma levels of soluble RAGE, we noted that the levels of AGEs and AOPP were trending toward higher values in patients with ALS as compared to controls. The increasing trend of AGE levels in plasma of ALS-affected patients is consistent with our own previous data showing an increase in tissue bound full-length RAGE and CML – one of the AGE representatives, in the spinal cord tissue of patients with ALS.[13]

Advanced glycation end products are naturally occurring products of nonenzymatic glycation and oxidation of proteins or lipids, presenting in low levels in plasma of healthy,

young and middle-aged individuals, and increasing during physiological aging and pathological processes such as atherosclerosis, diabetes, inflammation, and neurodegeneration.[34] Some studies showed that the excessive production and accumulation of AGEs exacerbates the inflammatory response, disturbs cellular metabolism, and increases cellular toxicity, leading to cellular malfunction, increased apoptosis and accelerated disease progression.[35,36] In neurodegenerative disorders, AGEs accumulation have been linked to an AGE-depended direct toxicity excreted on neuronal cells in cortex of patients with AD;[37] similarly, in Parkinson's disease, AGE-triggered cytotoxicity has been observed, affecting neuronal cell metabolism and reducing neuronal viability.[38] In ALS, significantly increased level of AGEs have been also observed in cerebrospinal fluid of patients with ALS and lower motor neuron disease compared to controls, but also to patients with AD, underscoring its potential as a diagnostic/prognostic tool in ALS.[39]

As with AGEs, AOPPs are the products of excessive oxidation, yet another of the pathological processes in which full-length RAGE plays a prominent role. Advanced oxidation protein products have recently gained attention as reliable markers of oxidation-triggered protein damage, including ALS.[40,41] It has been noted that RAGE, involved in the production of reactive oxygen species (ROS), plays a significant role in cellular damage and apoptosis driven by oxidation.[42]

Furthermore, the formation of AOPP through ROS triggers RAGE's detrimental role on cellular metabolism and long-term disfunction. Increased levels of AOPPs were first shown in the patients with chronic uremia.[43] However, subsequent studies demonstrated that their increase was not unique for uremic patients and they are also elevated in a wide array of pathological conditions, most notably, osteoporosis,[44] rosacea – which is a chronic inflammatory dermatosis,[45] psoriasis – yet another immunological disorder,[46] myasthenia gravis,[47] breast cancer,[48] and HIV.[49] Furthermore, a study by Siciliano et al. on antioxidant capacity and protein oxidation in ALS demonstrated a significantly increased presence of AOPPs in both plasma and cerebrospinal fluid of ALS patients, underscoring the importance of gaining a better insight into the role of oxidative stress in ALS pathogenesis and progression.[50] Consistent with these results, we also report elevated levels of AOPP in ALS and demonstrate that, similarly to AGEs, AOPPs are likely involved in ALS pathogenesis, signifying increased oxidative stress and oxidation-related cellular damage even in the early stages of the disease.

Conclusions

We report a decline of soluble RAGE concurrent with a rise of AGEs and AOPPs in plasma of ALS patients at the early stage of the disease. The results presented here suggest that a longer, longitudinal study of RAGE, AGE and AOPP plasma levels in ALS patients at different stage of the disease would be beneficial, outlining the dynamics between RAGE and its ligand levels as the disease progresses, thus making them likely diagnostic tools and potential therapeutic targets.

The results also indicate that further studies evaluating not only the plasma, but also cerebrospinal fluid levels of these substances would be warranted, providing new insights into their role in ALS pathogenesis and progression.

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