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Original Article

Etiology and treatment of amyotrophic lateral sclerosis

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Abstract: Background: To date all researchers conclude that the etiology of Amyotrophic lateral sclerosis (ALS) is not known. On the contrary, since August 2009, we believe that disease is of ischemic origin in the anterior surface of the medulla oblongata. Material and method: We present our surgical experience into 45 patients with ALS (bulbar form in 36 cases and spinal form in 9). Preoperative MRI scans revealed microinfarcts in the medulla oblongata and/or cervical cord. During surgery we found: 1) poor quality of omentum in most cases; 2) degenerative changes in the cervical spine; 3) anatomical anomalies at the V4 segments of the vertebral arteries; 4) moderate to severe atherosclerosis at both V4 segments; 5) unilateral absence or stenosis in the anterior-ventral spinal arteries (AVSAs). All patients received omentum on the anterior, lateral and posterior surface of the medulla oblongata, and in 9 cases, an additional segment at the C5-C6 level. Results: Neurological improvement was better during the first days or weeks after surgery than in the following months or years, in all patients. However, 13 patients suffered neurological impairment in about 4 months later, due to greater deterioration of the cervical spine, by contrast, 7 patients with mild ALS have experienced neurological improvement by 80 to 100% during a follow-up of 4 and 6 years. Conclusions: These results confirm that ALS is of ischemic origin in the intraparenchymal territory of the AVSAs and/or in anterior spinal artery caused by atherosclerosis and associated to anatomical variants in the V4 segments of the vertebral arteries. Because in contrast to this, its revascularization by means of omentum can cure (mild degree) or improve this disease.

Keywords: Amyotrophic lateral sclerosis, cervical degenerative changes, cervical spondylotic myelopathy, anterior-ventral spinal arteries, anterior spinal artery, omental transplantation

Introduction

To date, many researchers without knowledge of the etiology of amyotrophic lateral sclerosis (ALS), they use a stem cell transplantation by intraspinal or intravenous injection for the treatment of this disease [1, 2]. Because the used cells are patient's owen and therefore, there is no risk of rejection or side effects. Conversely, based on neurosurgical experiences with omental transplantationfor some "neurodegenerative diseases "[3-5] and cervical degenerative disease [6, 7]; we believe that ALS is of ischemic origin located in the intraparenchymal territory of the anterior-ventral spinal arteries (AVSAs) and/or anterior spinal artery (ASA) [5, 8-10].

We present the clinical and surgical results into 45 patients with ALS who received omental transplantation on the anterior surface of the medulla oblongata. In all of them was neurological improvement from the first days of the operation; but few months later, some patients had neurological deterioration. So that, the goal of this article is to analyse these results in a greater number of patients with ALS.

Material and method

Clinical cases

Between August 2009 and December 2016, we have transplanted omentum into 45 patients with definitive diagnosis of ALS [11-14], whose ages ranged from 33 to 81 years (mean age, 53.8): bulbar ALS in 36 cases and spinal ALS in 9. Most of patients with bulbar ALS, were admitted on moderate or severe degree (stages III to IV) and it was characterized by foot and leg cramps unilateral or bilateral followed by loss of strength in lower limbs and/or upper limbs.

Figure 1. Preoperative MRI scan of a 51-year-old man with pain neck and shoulder, showing severe cervical degenerative changes. Ten months before the onset of ALS, he was operated by cervical spondylosis.

Figure 2. Preoperative MRI scan of a 50-year-old woman with bulbar ALS, showing degenerative changes and microinfarcts in the cervical cord. She presented moderate tetraparesis, diffuse fasciculations, and light dysarthria.

Bilateral peripheral facial paresis, moderate or severe dysarthria, mild or moderate dysphagia, moderate or severe weak voice, inclination of the head, weakness in the respiratory muscles during the inspiration, fasciculations and moderate paresis in the tongue, malnutrition or weight loss, tetraparesis (spastic in lower limbs and flaccid in the proximal portion of the upper limbs), moderate or severe hypotrophy in the muscules of the scapulohumeral waist in all patients with spinal ALS, fasciculations in chest and abdomen, as well as in the upper and lower limbs, anemia and constipation. Only four patients were admitted with bulbar symptoms (dysarthria, dysphagia and fasciculations in the

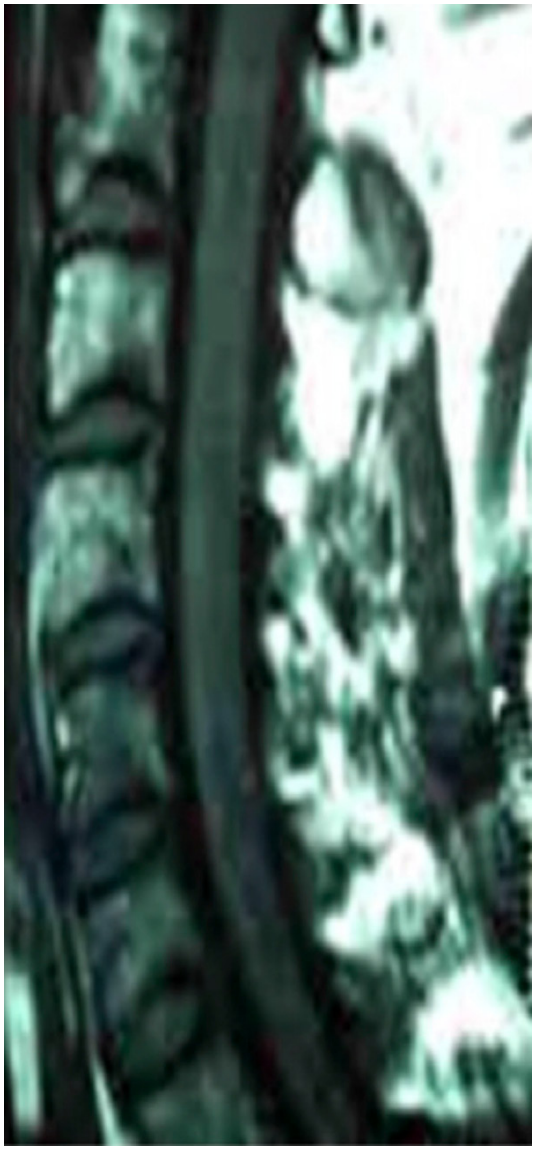

Figure 3. Preoperative MRI scan of a 55-year-old man with spinal ALS, showing severe cervical degenerative changes and microinfarcts in the lower cervical cord. The patient was admitted with normal gait and brachial amyotrophic diplegia.

Figure 4. A cervical spine X-ray, showing anterior fixation in a 51-year-old man due to cervical degenerative disease. However, two months after surgery, he presented clinical data of ALS.

tongue) without motor deficit in limbs. The onset of the symptoms in spinal ALS was charaterized by progressive brachial diparesis and muscular hypotrophy in scapulohumeral waist, and months or years later, they presented spastic paraparesis and then, bulbar symptoms. Only 7 patients with bulbar ALS were admitted at an early stage, while in the rest of cases, the definitive diagnosis was late. Previously, almost all the patients were consulted by several neurologist, even in specialized centers. No patient with tracheotomy or gastrostomywas admitted. Five patients had besides, type 2 diabetes mellitus. Ten of 45 patients also suffered fits of apneafor a few seconds associated with arterial hypotension, between 2 to 4 years before admission. Apnea was triggered by stress or moderate physical effort.

In 37 (82.2%) of these 45 patients, preoperative magnetic resonance imaging (MRI) scansshowed degenerative changes in the cervical spine in moderate or severe degree (**Figure 1**) characterized by osteoporosis in the vertebrae,

osteophytes, height reduced of the discs, several herniated discs, spondylolisthesis, spinal canal stenosis and hypertrophy of yellow ligament, among other findings. Likewise, in these 37 patients, preoperative MRI scans also showed doubtful or evident zonesof microinfarcts in the medulla oblongata and cervical cord (**Figure 2**) and very evident in patients with spinal ALS (**Figure 3**). Likewise in 21 patients, MRI scans without contrast revelead atherosclerosis at the basilar artery and/or at the V4 segments of the vertebral arteries. Hypotrophy of the pyramids in 18 cases, as well as hypotrophy of the frontoparietal cortex in 12 cases. The electrodiagnostic tests revealed denervation and fasciculations, among other findings, in all patients. Prior to this study, no patient was clinically diagnosed. On the contrary, in my opinión, the diagnosis of ALS is clinical and the imaging studies (CT, MRI, SPECT or PET) are of little help [10, 15].

At the time of admission, 12 patients had already undergone surgical liberation of the cervical cord and its roots, by means of an anterior approach (**Figure 4**) or via laminectomy. Because the patients presentedclinical and radiological data of cervical degenerative disease [16-20]. That is, in addition to the MRI findings, these 12 patients had neck pain with or without radiation to shoulders, paresthesia in arms, limitation of lateral movement of the head and fasciculations in the scapulohumeral waist. Based on previous experiences [5, 8], an omental transplantation to the medulla oblongata was proposed to the patients and their family, and before surgery, the patient's status was recorded on videotape.

Operation

Thesurgery was performed in two stages under general anesthesia: First, supraumbilical laparotomy to remove a segment of omentum and then, cervical laminectomy at the C1-C2 and C5-C6 (only in 9 cases) levels [5, 8, 21, 22]. During the laparotomy, in 36 patientsthe omentum was of poor quality; because this tissue was found thickened, pale and greasy (milky spots), ovoid, rounded, and poorly vascularized. A patient had not major omentum, because he havebeen suffered colon surgery several years ago, for this reason, we obtained almost all the minor omentum. This anatomical finding was informed to family members before surgery in the neck.

The medulla oblongata and cervical cord at C5-C6 level, was located as previously described technique [5, 8, 10, 21, 22]. During surgery we found: 1) hypertrophy of the posterior arc of atlas and spinous process of the axis; 2) hypertrophy of the yellow ligament; 3) inestability of the cervical spine; 4) anatomical variants of the V4 segments of the vertebral arteries; 5) moderate to severe atherosclerosis in both V4 segments; 6) absence or unilateral stenosis of the AVSAs, 7) several exsanguinated shorth and long circumferential arteries (arterial branches originated from the AVSAs and/or ASA); 8) several perforating arteries bloodless over the surface of the medulla oblongata; 9) hypotrophy of small nerve roots in the row of IX, X and XI cranial nerves, and 10) hypotrophy of the anterior roots at C5-C6 level. A segment of omentum was placed on the anterior (piramidal decussation and bulbar pyramids), lateral and posterior surface of the medulla oblongata and fixed to the dura mater by its inner face, and into 9 patients of this group, they received an additional segment of omentum on the anterior, lateral and posterior surface of the cervical cord (at C5-C6 level) by spinal ALS. In all cases, the dura matter was laxly faced and not to water seal. Two patients had transient arterial hypotension during the surgery and no bytrans-operative bleeding.

Thirty-five patients were extubated in the operating room. Eight patients were extubated in the intermediate care room between 1 and 4 hours after surgery due to weakness in the ventilation. One patient remained at intensive care unit by one day, and the other patient, during three weeks by respiratory complications. These 10 patients had malnutrition and/or severe ALS. Moreover, almost all patients left the operating room with nasogastric and Foley tube for 2 and 4 days. The nasogastric tube to receive liquid feed and hydratation.

Results

Neurological improvement (in different degrees) was observed in all patients since the first days of the operation. This improvement was better during the first days and weeks after surgery than in subsequent months or years. This improvement consisted in greater intensity of voice, in thedysarthria and swallowing movement, reduction of spasticity and fasciculations, improvement of motor movement in

Figure 5. Postoperative MRI scan of the same patient of **Figure 2**, performed six months after omental transplantation by neurological deterioration. The study shows more impairment of the cervical spine and canal.

limbs. Into 8 patients, the fits of apneadisappeared and blood pressure was normalized, who received omentum on the piramidal decussation. The hyperglicemia in 5 patients with type 2 diabetes mellitus not changed after surgery. Physiotherapy began from the first day of surgery and it was performed by the patient himself, with the purpose of improving the functional of the residual corticospinal and corticobulbar pathways, as well as of neurons in the motor nuclei of anterior horns of the spinal cord and muscles. In other words, to improve the function of residual nervous tissue in the intra parenchymal territory of the AVSAs and ASA [4, 5, 13, 23, 24].

However, 13 patients with cervical degenerative disease presented different degrees of neurological impairment in about 4 months after surgery. In 9 patients postoperative MRI scansrevealed to the omentum on the medulla oblongata, although smaller than the omentum placed during surgery (**Figure 5**), and in a man with brachial amyotrophic diplegia, the cervical MRI scan showed to the omentum outside the intradural space. We believe that the output of the omentum to the epidural space was secondary to the effort during defecation, because the patient suffered of chronic constipation before the surgery. Three patients with advanced ALS of 51, 70 and 81 years of age, they died during theirhospitalization caused by pneumonia. A 51 year-old. mandied in his bedroom, five days after surgery. This patient was eating solid food, and also abruptly presented 3 fits of apnea, sweating and hypotension in his bedroom, but the last was fatal. During the last crisis, a chest X-ray revealed only small infiltration in the lower lobe of the right lung. Other patient, a 70-year-old woman, died 3 weeks after surgery due to chronic constipation, lack of appetite and pneumonia.

On the contrary, seven patients with bulbar ALS (in mild degree) have neurological improvement experienced between 80 to 100% during a following of 4 to 6 years, and currently, all of them are working. In these 7 patients, the omentum was of good quality, ie., smooth, malleable, moderate thick and with abundant blood vessels [10, 25].

Discussion

These results confirm our previous observations [5, 8-10], that the etiology of this disease is of ischemic origin in the intraparenchymal (bulbar pyramids; piramidal decussation; ambiguus nuclei; the ventral respiratory groups or expiratory centers; the A1/C1 cell groups (related with the arterial pressure); dorsal motor nuclei of the vagus nerves; facial nuclei; hypoglossal nuclei and nucleus of the solitary tracts, especially the ventro-lateral portions, also known as the dorsal respiratory groups or inspiratory centers, among others) territory of the AVSAs whose normal average diameter is of 0.75 mm, and/or ASA with an average diameter of 0.80 mm up to about T1 level [5, 13, 24, 26, 27]. Therefore, this disease is not neurodegenerative; because it can be cured (mild stage) or improved (moderate or severe stage) through an omental transplantation on the anterior surface of the medulla oblongata. A conclusion

contrary to most researchers, who continue to support that ALS is a neurodegenerative disease, and therefore has not cure. But more and more new scientific contributions support our results, particularly in relation to the etiological agent.

In 2004, based on neurosurgical experiences with omental transplantation,one of us published a hypothesis about the neurodegenerative mechanisms [3, 4]. Hypothesis supported currently by several authors [28-30], that the neurodegenerative process is secondary to the formation of free radicals and oxidative stress in the ischemic area; provoking an imbalance between the oxidant and anti-oxidant (endogenous defenses) systems, in favor of the oxidants [3, 9, 15, 31]. Under normal biochemical and physiological conditions in any area of the brain, the levels of free radicals are controlled by enzymes such as catalase, glutatione peroxidase and various types of superoxide dismutase, among other endogenous defenses (anti-oxidants) which prevent the process of oxidative stress, ie., irreversible damage to intracellular biological molecules such as DNA, RNA, proteins and lipids [4, 15, 28, 1]. In this way in the nervous tissue in ischemia and ischemic penumbra by atherosclerosis and/or the influence of environmental chemicals (cigarette smoking, pesticides and organic solvents, etc) [3, 4, 9, 15, 28], a normal neuron with aerobic respiration, it turn into in other ischemic neurons with anaerobic respiration, associated with a decrease of ATP, loss of control of cell membrane and increased free radicals formation. Then, both factors (atherosclerosis and toxic agents) directly or indirectly increases the formation of free radicals, followed by oxidative stress, neurodegeneration and finally, localized or diffuse atrophy [4, 9, 15]. Therefore, the use of exogenous anti-oxidants (Resveratrol, Vit A, Vit C and Vit E, etc) and/or the stem cell transplantation by intraspinal or intravenous injection for the treatment of ALS [32, 33], could be of little utility; because the ischemic areas (intraparenchymal territory of AVSAs and ASA) would not receive these substances nor transplanted stem cells. However, vascular recanalization through aspirin may allow exogenous antioxidants to enter the ischemic areas [15]. That is, without vascular recanalization or revascularization in the ischemic zones, residual neurons no re-send axons to specific areas already establised, ie., no neuronal regeneration or neurogenesis occurs [15].

Likewise, we believe that the disappearance of the fits of apnea and normalization of blood pressure was due to revascularization of respiratory and cardiovascular centers in the medulla oblongata. That is, through our surgical method, we revascularize the inspiratory centers (ventrolateral group of the solitary nucleus), expiratory centers (ambiguus and retroambiguus nuclei),and probably to the apneustic center; as well as to the cardiovascular reflex center (caudomedial and commissural portions of the solitary nucleus) and to the A1/C1 cell groups related with the blood pressure [5, 10].

Thus, the revascuarization of the ischemic areas by means of the omentum, improves the function of the residual nervous tissue in the affected zone [5, 8, 9]; because the omentum produces new blood vessels from 6 hours of the implant and through them, the ischemic zone and surrounding areas receive nutrients (amino acids, carbohydrates, lipids, vitamines and minerals), oxygen, neurotransmitters, neurotrophic factors, adipocytokines and omental stem cells [25, 34, 35]. Therefore, the omentum favor the neuronal regeneration, neurogenesis (neurons of short axon) and gliogenesis in the affected zone; because it receives directly mesenchymal stem cells from the omentum [34, 35]. Thereby, the best results could be achieved in patients with mild ALS and using omental tissue of good quality.

On the other hand, we believe that the neurological deterioration observed in 13 patients to a few months after surgery, it was due to one or more factors such as: 1) poor quality of the omentum; 2) malnutrition and low hemoglobin in the bloodstream; 3) severe atherosclerotic changes in the aortic arc, carotids and vertebrobasilar system [15, 33, 36, 37], and 4) degenerative changes in the cervical spine (**Figure 5**) caused by progressive ischemia at the arterial branches originating from the V1 and V2 segments of the vertebral arteries [19, 20, 26, 32, 38, 39], in particular of the anterior radicular arteries (anastomotic branches with the ASA at C5 to T1 level) [13, 24, 26, 33, 39]. In other words, cervical spondylosis is a disorder caused by progressive ischemia in the cervical vertebrae (spongy osseous tissue), but occurs most frequently at the C5-C7 region where there is the greatest degree of flexion [7, 17].

Consequently, cervical degenerative disease [13, 16, 18-20, 39], cervical spondylotic myelopathy [6, 17, 40] and ALS [8, 5, 9, 10]; all of them are caused by progressive ischemia in the cervical spine due to atherosclerosis [15, 20, 36, 37], and associated with anatomical variations at the vertebral arteries and its branches [15, 24, 32, 33, 38]. In the first, the ischemia affecting to the cervical vertebrae [22, 39, 40]; in the second, vascular impairment extends in the cervical cord through the anterior and posterior radicular arteries [12, 20, 24], and in the third, the progressive ischemia affecting the intraparenchymal territory of AVSAs and/or of ASA, but in the lower cervical cord. Of the three diseases, the two firsts are the most common and both can also be treated which omental transplantation [7, 19].

Conclusions

Our results confirm that the etiology of ALS is of ischemic origin, especially in the intraparenchymal territory of AVSAs caused by atherosclerosis and associated to anatomical variants at the V4 segments of the vertebral arteries. Since, by contrast, its revascularization by means of the omentum produce neurological improvement in variable degrees, from the first days of surgery. By contrast, we believe that the neurological impairment occurred in some patients, is related with the poor quality of the omentum implanted, increases of atherosclerosis in the vertebral arteries and/or vertebral-subclavian junction, and higher degenerative changes in the cervical spine. Finally, we want to add, that the diagnosis of this disease is essentilly clinical and helped with electromyography. For this reasons, future studies of autopsy in the cervical cord and medulla oblongata of ALS patients are needed to confirm our surgical findings and postoperative results.

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