

Review Article

Omental transplantation for neurodegenerative diseases

Hernando Rafael

Academia Peruana de Cirugía, Lima, Peru

Received April 2, 2014; Accepted August 3, 2014; Epub September 6, 2014; Published September 15, 2014

Abstract: Up to date, almost all researchers consider that there is still no effective therapy for neurodegenerative diseases (NDDs) and therefore, these diseases are incurable. However, since May 1998, we know that a progressive ischemia in the medial temporal lobes and subcommissural regions can cause Alzheimer's disease; because, in contrast to this, its revascularization by means of omental tissue can cure or improve this disease. Likewise we observed that the aging process, Huntington's disease, Parkinson's disease, and Amyotrophic lateral sclerosis; all of them are of ischemic origin caused by cerebral atherosclerosis, associated with vascular anomalies and/or environmental chemicals. On the contrary, an omental transplantation on the affected zone can stop and improve these diseases. For these reasons, I believe that NDDs, are wrongly classified as neurodegenerative disorders.

Keywords: Aging, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, omental transplantation

Introduction

Up to now, neurodegenerative diseases (NDDs) are defined as hereditary and sporadic conditions, which are characterized by progressive nervous system dysfunction, ie., when neurons in the brain and spinal cord begin to deteriorate. Thereby, almost all researchers conclude that NDDs are incurable and debilitating conditions that result in progressive degeneration and/or death of neurons [1-3]. By contrast to these conclusions, my colleagues and I have a different opinion, based in neurosurgical experiences into patients with NDDs whom received omental transplantation (Free graft with vascular microanastomoses) [4-6].

We choose the omentum, because it is the best tissue for developing vascular connections with underlying and adjacent zones, and through these neovessels (revascularization), the affected nervous tissue receives an increase in blood flow, oxygen, neurotransmitters, neurotrophic factors, adipocytokines, and omental stem cells [4-7]. Thus, the function of neurons and axons in the residual tissue in ischemia and ischemic penumbra improvement and later on, because of neuronal regeneration [8, 9]

and neurogenesis [7-11]. In 2004, I presented a hypothesis (**Figure 1**) about the neurodegenerative mechanism caused by cerebral atherosclerosis and action of environmental chemicals in specific zones of the encephalon, in order to cause the so-called NDDs [5]. Now, I present to a group of patients who were treated previously as NDDs and after omental transplantation, all of them experienced neurological improvement.

Aging

Biological aging is a process opposed to growth and development in a person, which produce physical, psychological and social changes with age; due to a gradual loss of cells in all parts of the body, especially in skin, cardiovascular system, nervous system and connective tissue, among other systems. There are several theories on the cause of aging, from to be programmed in the genes and the radiation solar, on the other hand. However, in 1981 was reported the evidence most convincing about a direct correlation between decreasing growth hormone (GH) levels and the aging process [12], and nine years later on, the same authors reported rejuvenation in persons over 60 years

Omentum for neurodegenerative diseases

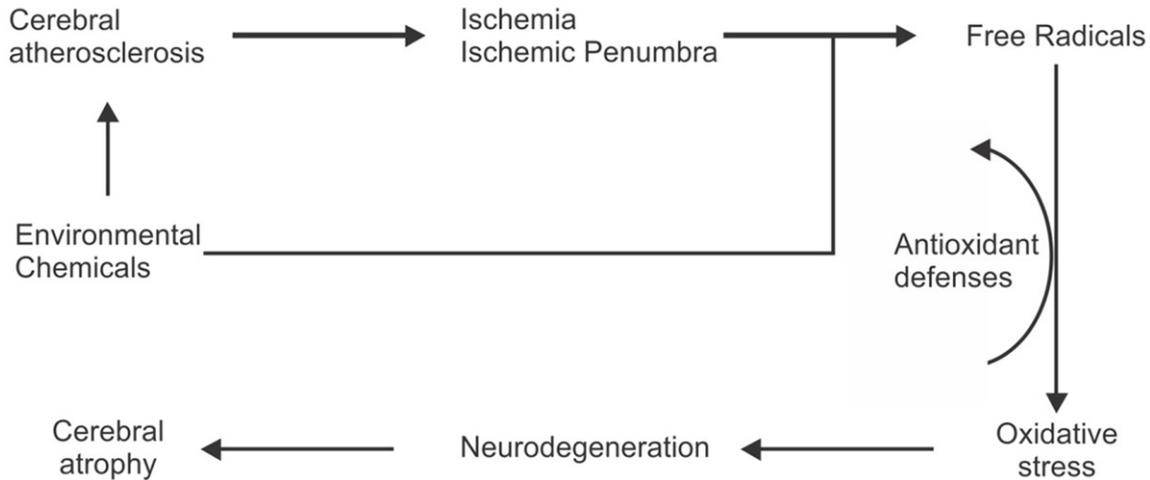


Figure 1. Ischemic events occurred in the affected zone in each one of NDDs. Before the Neurodegenerative process occur the formation of free radicals, and the oxidative stress is caused by an imbalance between the oxidant and antioxidant (endogenous defenses) systems in favor of the oxidants.

of age after the subcutaneous administration of biosynthetic human GH [13]. Since then and to date, four therapeutic methods are used against aging: 1) administration of exogenous GH; 2) administration of exogenous growth hormone-releasing hormone (GHRH); 3) administration of secretagogue products, and finally, 4) hypothalamic revascularization [13-16]. The fourth therapeutic method is based in histological and neurosurgical observations into the producing hypothalamic nuclei (lowermost portion of the ventromedial nuclei, arcuate nucleus and both tuber cinereum) of GHRH [15-20]; especially the arcuate nucleus constituted by GHRH, Luteinizing hormone releasing hormone (LHRH), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) and proopiomelanocortin (POMC) neurons, as well as ependymal cells and tanocytes [16, 21]. For these reasons, to exist regressive changes in the arcuate nucleus with the aging [17-20] and by contrast, rejuvenation after omental transplantation on the optic chiasma, carotid bifurcation and anterior perforated space (APS) [15, 16, 21]; I believe that the aging process must also be considered as neurodegenerative disease. In the **Figure 2**, I diagram the pathophysiology and treatment of the aging process. This disease [22] is initiated in the arcuate nucleus by progressive ischemia, due to atherosclerotic plaques located at the mouths of the collateral branches (especially of the superior hypophyseal arteries) originating from the supraclinoid carotids [15, 21-23] and associated to anatomical variants of the circle

of Willis [20, 24, 25]. Thus, the synthesis and secretion of GHRH and LHRH decline with age.

Since the first patient reported [15] and to date [21]; we have analysed the rejuvenation into 38 patients whom received omental transplantation on the carotid bifurcation and APS. In 32 (84.21%) of 38 patients, we observed different degrees of rejuvenation and in the rest, the changes were uncertain or null. The scarce or absence of clinical data of rejuvenation into the other 6 patients was related with dilation of the third ventricle [21]. These results indicate that the degree of rejuvenation is related with the amount of neurons in the arcuate nucleus and its functional recovery, after the revascularization by means of the omentum. In addition to this, I think that neurogenesis in the arcuate nucleus and adjacent areas may be provoked by omental stem cells [7, 11] and neural stem cells starting from undifferentiated cells located in the subventricle zone (SVZ) [10, 26, 27]; especially mesenchymal stem cells derived from the omentum, because seems that neural stem cells in the hypothalamus are scarce or do not exist [22, 28]. That is, we can induce neurogenesis and neuronal regeneration in the arcuate nucleus [9, 21, 28, 29], after to place omental tissue on the carotid bifurcation and APS. For these reasons, unlike the three first therapeutic methods against aging [16, 21], our surgical procedures improvement the function of the residual arcuate nucleus and adjacent zones. Therefore, hypothalamic revascu-

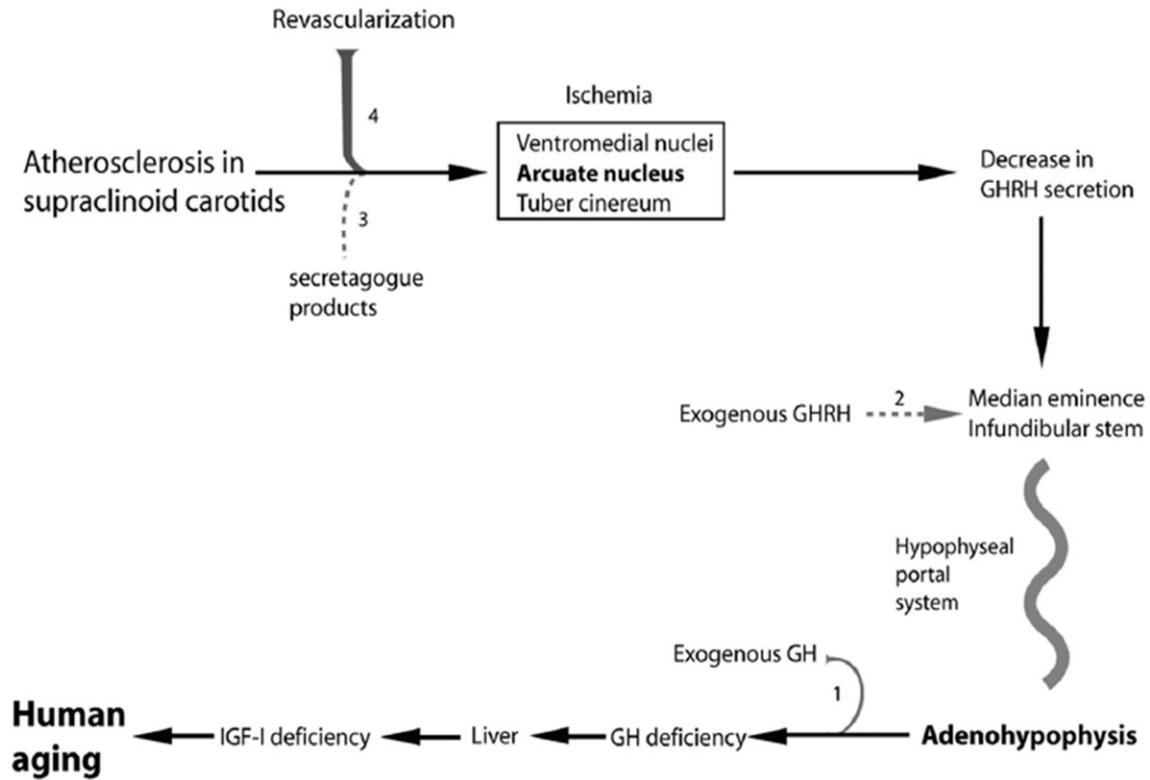


Figure 2. Schematic representation of the aging process and its treatment. GH, growth hormone. GHRH, growth hormone-releasing hormone. IGF-1, insulin-like growth factor-1. Hypotalamic revascularization favours the synthesis and secretion of endogenous GHRH and GH. Adapted from reference 16.

larization against aging is a reconstructive or physiological method.

Huntington's disease

All researchers inform that Huntingto's disease (HD) is a neurodegenerative genetic disorder in about 90 to 95% of cases and in the rest, it are sporadic cases [30-32]. The genetic defect on the short arm of chromosome 4 was reported in 1983 by Gusella and colleagues [33]. Mean age at onset of symptoms is between 30 and 50 years [34], but can begin at any age from infancy to old age. When the disease onset before age 20, the condition is called juvenile HD. The early stage (mild HD) of this disease is characterized by 1) uncontrollable movement of the arms, legs, head or face so-called chorea (typical course, because this symptom is the cardinal change of HD) or 2) behavioral and personality changes (atypical course) characterized by depression, irritability, anxiety and hallucinations, among other psychiatric changes. Both data as initial symptoms [5, 30, 34-36]. To date, all authors conclude that there

is no cure for HD [30, 32, 34]. Some authors have performed medical treatment with tetra-benazine [37], and surgical procedures such as transplantation of embryonal [38] or fetal [39, 40] striatum into both the caudate and putamen of HD patients. Likewise, other authors have used stem cells therapy [41] and deep brain stimulation [42] into the striatum in patients with HD. These medical or surgical procedures can help manage some of the symptoms, but can not slow down or stop this disease.

Based in an anatomo-clinical correlation [36, 43]; we have used omental transplantation to treat this disease. Case 1, on July 1999, my colleagues and I transplanted omental tissue to a 35-year-old man with advanced HD, characterized by to be confined to bed, decorticate posture, bruxism, severe dysarthria, difficulty swallowing, lack of concentration, short-term memory impairment and choreic movements in the hands, feet, face and trunk [36]. In addition to these neurological data, the patient was malnutrition. Moreover, the patient had 9 close



Figure 3. Postoperative CT scan with contrast obtained 3 months after surgery, showing the presence of omental tissue over the left sphenoid ridge, optic chiasma, carotid bifurcation and anterior perforated space, in a 75-year-old woman with mild AD. Adapted from reference 70.

relatives (maternal grandmother, mother, five of seven brothers, an aunt and a niece) with the same disease. In 8 of these families, the disease began between the ages of 25 and 38 years [36]. A preoperative computed tomographic (CT) scans revealed atherosclerosis of the circle of Willis and symmetrical dilation of the ventricular system with atrophy of the caudate nuclei [21, 36]. In the same way, we observed atherosclerosis in the supraclinoid carotids as well as the circle of Willis on CT studies in another three familial cases of HD [44]. Case 2, on March 2008, we operated other patient with sporadic HD. A 70-year-old woman with mild HD [45] for the prior 10 years experienced depression and attempted suicide. Four years later, she presented choreiform movements which increased with stress and decreased during sleep. A preoperative CT scans and magnetic resonance imaging (MRI) revealed atherosclerosis of the supraclinoid carotids (or C4 segments of the internal carotid arteries), slight cortical atrophy, and slight atrophy of the caudate nuclei.

Through a left pterional-transsylvian approach in both cases, we located the supraclinoid

carotids [36, 45, 46]. During surgery, we made important observations: 1) moderate atherosclerosis of the supraclinoid carotids and its terminal branches; 2) exsanguinated and collapsed Heubner's recurrent arteries (Case 1) or absence of the left Heubner's recurrent artery (Case 2); 3) absence of the anterior communicating artery, and 4) several exsanguinated and collapsed anterior perforating arteries. The omentum was placed on the optic chiasma, the carotid bifurcation and APS [36, 44]. The patients experienced improvement beginning 12 hour after surgery (Case 2) and third postoperative day (Case 1). Up to six months after operation, the first patient showed moderate improvement of the choreic movements, he experienced improvement in short-term memory, his mastication and swallowing were almost normal and he walked with or without assistance. However, the patient died suddenly as a result of aspiration pneumonia. In this patient, neurological improvement was better during the first weeks after the surgery than in the ensuing months. In the second patient, the choreiform movements decreased, and her facial expression improved 50%. However in approximately 21 hours after surgery, the patient died at the hospital due to a post-traumatic cerebral hemorrhage. This woman attempted to walk without assistance, but she suffered fallen and craneal trauma.

These clinical, tomographic and surgical findings indicate that the early stage of HD is caused by progressive ischemia in the intraparenchymal territory of the Heubner's recurrent and/or anterior perforating arteries, as result of atherosclerotic plaques located at the mouths of these arterial branches, and associated to anatomical anomalies of the circle of Willis [5, 24, 36, 47]. Because, in contrast to this, the function of the residual nervous tissue in the setting of ischemia and ischemic penumbra can improve if the circulation through the omentum is restored and later, because of neuronal regeneration [44, 45, 48] and neurogenesis [7, 10, 41]. Neurological improvement in the case 1, is beyond doubt an example of absence of the genetic factor in this disease. By contrast, we believe that the genetic factor may be related with anatomical anomalies of the circle of Willis [24, 47, 49-51] and a predisposition of the endothelium of these vessels toward some toxic agent [34, 35, 52-54].

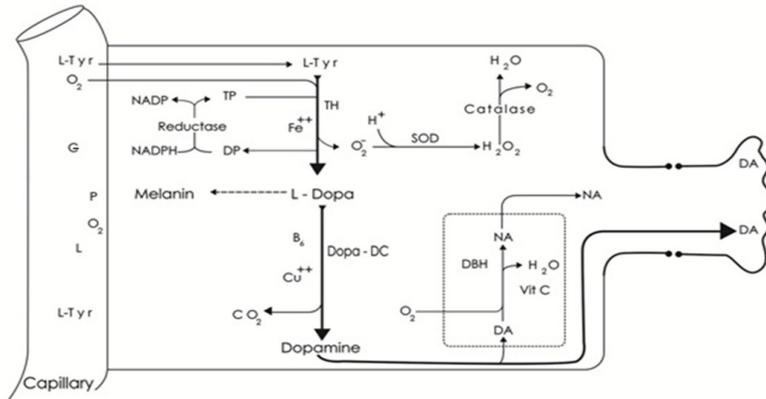


Figure 4. Biosynthesis of dopamine (DA) and noradrenaline (NA) in a catecholaminergic neuron. L-tyrosine (L-tyr), molecular oxygen (O_2), tetrahydropteridine (TP), superoxide radical (O_2^-), superoxide dismutase (SOD), Dopa decarboxylase (Dopa-DC), dopamine beta hydroxylase (DBH), glucose (G), proteins (P), and lipids (L) are shown. Therefore, a decrease in blood flow in the capillary is the key in the pathogenesis of PD. Adapted from references 108 and 120.

Therefore, although all researchers affirm that HD is an autosomal dominant inherited disease and there is no cure [30, 31, 34, 39]; the post-operative evolution of our patient with familial HD [36, 44] put in doubt this asseveration. On the contrary, we believe that this disease is caused by progressive ischemia, in the intraparenchymal territory of the recurrent arteries of Heubner (head of the caudate nuclei and rostral portion of the putamen) [49-51] and anterior perforated arteries [36, 49]. Thus, the deterioration of the blood flow in the recurrent arteries provoke abnormal and unusual movements, whereas the subcommissural regions are involucrate with psychiatric disturbances [5, 34, 36, 42, 48].

Alzheimer's disease

There are two types of Alzheimer: 1) Primary Alzheimer or Alzheimer's disease (AD), whose cause is not known [55-57], and 2) Secondary Alzheimer, to previous atherosclerosis at the supraclinoid carotids and circle of Willis is associated with inflammation in the chiasmatic cistern due to traumatic brain injury [58, 59], cysticercosis [60-62], cryptococcal [63-65], and tuberculous [65] meningitis, among other factors. So, the collateral arteries of the supraclinoid carotids can be affected by mild to severe basal exudate [64, 65]. AD is considered as a progressive brain disease and classified also, as neurodegenerative disorder.

Between January 1998 and July 2013, we have attended to 192 patients with AD. There were 148 women (77.08%) and 44 men (22.92%), especially were postmenopausal women [66-68]. Unlike the clinical criteria established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the AD and Related Disorders Association (ADRDA) for the diagnosis of AD [69]; since 1999, we used a viewpoint different [66, 68, 70]. First, the 192 participants were divided into three groups with regard to

its clinical variety: Sporadic cases (76.05%); uncertain cases (17.70%), and 3) familial cases (6.25%). That is, the 93.75% of AD patients were non-genetic cases. Second, as the clinical findings appeared of manner sequential and progressive, the clinical stage was divided in mild (52 cases), moderate (108 cases) and advanced (32 cases) degree. We put special attention to the transition zone between "normal aging" and the onset of the symptoms [16, 56, 71]. The prospective and retrospective analysis performed of the early stage (mild AD) in the 192 participants, it was characterized by; 1) progressive loss of recent memory in 75% of cases (typical course, because this symptom is the cardinal change of AD), and 2) behavioral and personality changes in 25% (atypical course). Both data as initial symptoms, and with less frequency, associated with olfactory and gustatory (16.60%) or visual (7.80%) deficit, among other symptoms as insensitivity to pain and temperature, insomnia, isolation, anxiety, somnolence and depression, etc. In all cases, the onset of the symptoms was insidious, course undulating (periods of clinical improvement alternated with those of worsening) and progressive.

In the 52 mild AD patients, the CT and/or MRI scans showed two important findings. First, normal cerebral parenchyma or slight cerebral atrophy that was normal for the age, and Second, atherosclerosis at the supraclinoid

carotids, the circle of Willis and at the basilar artery. On the contrary, neuropsychological tests in 136 patients revealed clinical data of dementia. Therefore, the diagnosis of mild AD was clinical and by contrast, auxiliary studies as CT and MRI scans proportioned little aid [66, 68, 70-74]. In addition to the clinical data of mild AD; the 108 moderate AD patients presented [66, 70, 74, 75]: 1) slight or moderate impairment of higher cortical functions (aphasia, apraxia, agnosia); 2) posture and/or gait disturbances; 3) motor and sensory impairment; 4) the diagnosis of dementia was obvious, and 5) slight or moderate cerebral atrophy demonstrated by CT and/or MRI scans. Other auxiliary studies as single photon emission computed tomography (SPECT) were observed only in 8 cases. CT scans findings demonstrated atherosclerosis at the supraclinoid carotids as well as at the circle of Willis. In the familial AD patients [67, 76], the tomographic findings were similar to the sporadic AD cases. The 32 advanced AD patients was characterized by severe disturbances of motor, sensory or sphincter functions and associated to be confined to bed, malnutrition and weight loss. CT scans showed severe cerebral atrophy [66, 70].

Of the 192 patients attended, only we have transplanted omental tissue in 29 patients. Eight cases with mild AD and 21 with moderate AD, in accordance with a surgical technique published previously by us [46, 70, 74, 75, 77]. Carotid bifurcation and the APS were located through a pterional-transsylvian approach. During surgery we found: 1) moderate or severe atherosclerosis in the supraclinoid carotids; 2) anatomical variants in the anterior choroidal and anterior perforating arteries; 3) a variable number of exsanguinated and collapsed anterior perforating arteries; 4) some perforating branches with residual blood flow centripetal to the origin of the vessels, and 5) cerebral atrophy within the surgical zone in the 21 patients with moderate AD, especially the medial temporal lobes. Previous end-to-end anastomoses by invagination between the superficial temporal vessels and the gastroepiploic vessels of the omentum [78, 79], the omental tissue was placed on the optic chiasma, carotid bifurcation and APS. Neurological improvement in our 8 patients with mild AD began on the first or third day after surgery and they remained symptom-free starting from two weeks. At pres-

ent several months or years later, their quality of life in 7 patients is good, they participate in activities of daily living similar to any normal persons of their age, and without medical treatment for AD. Moreover, all patients experienced rejuvenation [21, 70]. Likewise in the 21 moderate AD patients, we observed neurological improvement since the first days after surgery, and it was better during the first weeks than in the following months or years. The degree of improvement was different between the patients and currently, they present a neurological improvement about 50 to 80% in relation to preoperative clinical data [70, 74, 75]. Moreover, 18 of 21 patients experienced some data of rejuvenation.

We believe that the complete reversal (cure) of the symptoms in the mild AD patients was due to revascularization of the subcommissural regions (constituted by the substantia innominata, olfactor tubercule, islands of Calleja, diagonal band nuclei, nucleus accumbens, septal nuclei and fiber bundles) [43, 80], and medial temporal lobes (constituted by the hippocampal formation, entorhinal regions and the amygdaloid bodies) [81-83]. Shortly after this, secondary to neurogenesis in the underlying and adjacent zones to the omentum [7, 27, 70]. So, we think that the onset of the symptoms in AD are due to progressive ischemia in the intraparenchymal territory of the anterior choroidal [84, 85] and anterior perforating arteries caused by atherosclerotic plaques located at the mouths of these collateral branches originated from the supraclinoid carotids [70-72, 86]. In the **Figure 3**, I present a postoperative CT scans in a 75-year-old woman with mild AD who experienced cure of this disease [75, 77]. She was the first patient operated [77]. Likewise, our results indicate that neurological improvement observed in the 21 moderate AD patients was also due to revascularization of the residual nervous tissue (áreas in ischemia, ischemic penumbra and local atrophy) in diencephalic structures and surrounding zones. Therefore, neurological improvement is related, essentially, with the degree of morphological and functional recovery in the subcommissural regions and medial temporal lobes, due to revascularization, neuronal regeneration, gliogenesis and neurogenesis [7, 10, 27, 70, 87] in the affected áreas.

Thus, our surgical technique acts in the cholinergic and neuropeptidic nuclei to favor the synthesis of acetylcholine; whereas an omental transposition (pedicled graft) [88, 89] on the fronto-temporal cortex improvement only the axonic terminals and synaptic cleft of the cholinergic axons. Thereby our surgical procedure can cure (mild AD) or improve (moderate AD) this disease [70, 72, 74, 86]. A conclusion that confirms previous reports [73, 90-92] that there is a association between atherosclerosis of the circle of Willis with the pathogenesis of AD. In addition to this surgery, our patients receive aspirin and clonazepam.

Parkinson's disease

Parkinson's disease (PD) is a disorder of the brain that leads to tremors and difficulty with walking. There are two types of parkinsonism [93]: 1) Primary parkinsonism or PD whose cause is unknown [94], and 2) Secondary parkinsonism provoked by head trauma [95, 96], encephalitis [93], subdural hematoma [97, 98], pesticides and/or organic solvents [99, 100], and temporal lobe tumors [101, 102], among other factors. The viral agents and environmental chemicals acts directly into the dopaminergic neurons (**Figure 1**), while the head trauma, sudural hematoma and tumors provoke ischemia in the substantia nigra by distortion and stress to the midbrain. PD represent the 83.80% of all cases of parkinsonism [93] and to date, all researchers conclude that there is no cure for this disease [94, 103, 104].

But, based on neurosurgical experiences into PD patients [105, 106]; since September 1990, we have postulated that PD is caused by progressive ischemia in the intraparenchymal territory of the posterior perforating arteries due to atherosclerotic plaques located at the mouths of these arteries [107-110]. For this reason and unlike other neurosurgical techniques [103, 111-114]; since February 1988 to December 2004, we transplanted adrenal medulla and omentum to the putamen into 22 patients with moderate (17 cases) and advanced (5 cases) PD [105, 106, 115-118]. The adrenal medulla was implanted in the putamen by a transinsular pathway and the omentum was laid on the APS and insular cortex. Because a rapid and efficient revascularization of the donor tissues of catecholamines in the neostriatum, is an essential prerequisite to

improve function and prolong survival of the grafts [116-119] and thus, to facilitate the biosynthesis of dopamine and noradrenaline in the adrenal chromaffin cells implanted into the putamen [108, 117, 119, 120], as we showed in the **Figure 4**.

In all patients, a laparotomy and craniotomy were performed simultaneously. First, six to eight pieces of adrenal medulla were implanted in the putamen through the insular cortex, and after, the omental tissue was placed on the APS, insular cortex, medial temporal lobe and fronto-parieto-temporal cortex [106, 117]. In all patients, neurological improvement was observed since the first postoperative day and it was better during the first weeks after surgery than in the following months or years. Fifteen patients (70%) with grade 3 and 4 on the Hoehn and Yahr scale (H/Y scale), they remained symptoms-free for 6 years and without anti-parkinsonian therapy, and in the other 7 cases, they required antiparkinsonian medication.

Due to the failure of the transplant of catecholaminergic tissues into the putamen and/or caudate nuclei [103, 111-113] without omental transplantation; the researchers increase the use of other surgical techniques such as high-frequency deep brain stimulation into the thalamic ventral intermediate (Vim) nucleus for PD with tremor [121, 122], into the subthalamic nuclei to reduce the rigidity [123, 124], and in the globus pallidus internus [124]. Surgical techniques palliatives that only, they improve the tremor or rigidity, but not the disease (tremor, rigidity, bradykinesia, muscle pain, cramps, depression, speech disturbances and facial masking, among other signs) [93, 110, 117].

With the discovery of human mesenchymal stem cells (umbilical cord-derived and bone marrow-derived mesenchymal stem cells), the transplant of donor tissues of catecholamines (adrenal medullary, cervical sympathetic ganglion, fetal mesencephalic tegmentum and carotid body) was abandoned, but not the neurostimulation for PD [121, 122]. Likewise with the discovery of adipose-derived mesenchymal stem cells (about 2004), especially from the omental tissue [7, 125-127]; we proposed two surgical procedures to treat PD [109, 110, 119]: 1) omental transplantation on the interpeduncular fossa to revascularize the

dopaminergic nuclei (nuclei A8, A9, and A10) and surrounding structures in the early stages of PD, and 2) dual catecholamine-producing tissue and omental transplantation in moderate or advanced stages of PD. Moreover, researchers found neural stem cells located in the SVZ of the lateral ventricles and their migration as new neurons through intermediate zones up to the damaged cerebral cortex [10, 87, 128, 129]. However to prolong the survival of these new neurons in the nervous tissue in ischemia and ischemic penumbra, the cerebral zone must be revascularized with omental tissue.

Therefore, an omental transplantation on the ischemic zones in the intraparenchymal territory of the posterior perforating arteries, is the surgical method more appointed to favor the cell proliferation, migration and neuronal differentiation in the adult human encephalon. These, new neurons have two origins: 1) spontaneous neurogenesis starting from the neural stem cells located in the SVZ, and 2) neurogenesis provoked by omental stem cells (adipose-derived mesenchymal stem cells) [7, 28, 87]. Since October 2011 and December 2012, we have transplanted only, omental tissue into 3 patients with advanced PD [130]. The neurosurgical method was basically the same that the previously reported by us [46, 105, 106, 109, 115]. During surgery we found: 1) moderate or severe atherosclerosis in the supraclinoid carotids; 2) absence of anterior choroidal or posterior communicating arteries; 3) several exsanguinated anterior and posterior perforating arteries, and 4) severe atherosclerosis in the basilar bifurcation. An omental segment was placed on the supraclinoid carotids and APS, and other segment of omentum was placed on the interpeduncular fossa. Neurological improvement was observed after the third day and very evident in the first weeks postoperatively. At present, 16 to 26 months after surgery, two patients have experienced improved by 70 to 80% and with incomplete anti-parkinsonian medication. The third patient, a 64-year-old man with grade 3 of PD (on H/Y scale) present a neurological improvement by 90% that does not require anti-parkinsonian treatment. Beside, the 3 patients receives 500 mg of aspirin per day and 1 mg of clonazepam at night.

These results confirm that PD is caused by progressive ischemia in the intraparenchymal ter-

ritory of the posterior perforating arteries, due to atherosclerotic plaques located at the mouths of these arteries originated from the distal end of the basilar artery and its branches; because, in contrast to this, its revascularization by means of omentum produced neurological improvement of this disease.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is also considered a neurodegenerative disease that attacks the nerve cells responsible for controlling voluntary muscle. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, ceasing to send messages to muscles. Approximately 90 to 95% of persons with ALS have the sporadic form and in the rest of cases are familial [131, 132].

Charcot described ALS in 1874. He pointed out the unique involvement of lateral columns and anterior grey matter, and noted that these two areas of the spinal cord were closely connected. However, to date, almost all researchers conclude that the cause of ALS is not known [133, 134]. Several factors have been etiologically linked with ALS [134-136]; but recently, clinical evidences suggest that ALS is related with progressive ischemia in the intraparenchymal territory of the anterior-ventral spinal arteries (AVSAs) and/or anterior spinal artery (ASA) caused by atherosclerosis [137-140].

Many therapeutic management have been tried, including the rehabilitary [136]. Baclofen, a GABA derivate with anti-spasticity activity, and the riluzole, an anti-glutamatergic agent; both of them may aid ALS patients. Unfortunately, the response is scarce, often brief [132, 136]. Other authors have tried surgical management just as chronic cortical stimulation [141], bone marrow mesenchymal stem cells transplantation into the frontal cortex [142] and finally, bone marrow mesenchymal stem cells transplantation into the bulbo-medullary junction [143]. During the follow-up of 1 year after transplantation, nine of 13 patients experienced neurological improvement [143]. We, based on previous neurosurgical experiences with omental transplantation on the upper cervical cord and medulla oblongata for the treatment of infarct in the cerebellar hemispheres [144, 145]; primary occipital neuralgia [146], and for the treatment of sporadic olivo-

pontocerebellar atrophy [145, 147]; since August 2009 to December 2013, we have transplanted omental tissue [138, 140] into 24 patients with bulbar (18 cases) and spinal (6 cases) forms of ALS. During the admission, each case was rated on an arbitrary scale (scales I-V) based on the level of clinical data [136]. The stages of disease in these 24 patients was divided in stages II to IV. No patient with tracheotomy or gastrostomy was admitted. In 13 of 18 patients, the onset of the disease was spinal (characterized by paresthesia, spastic paraparesis or tetraparesis, brachial diparesis, fasciculations and gait disorder) and months later, they began with bulbar symptoms (dysarthria, dysphagia, hypotonic uvula, weak voice, fasciculations in the tongue and respiratory impairment). Moreover, six of our ALS patients had spinal onset, and without no bulbar symptom. Four of these 6 patients had Aran-Duchenne's hands.

CT and/or MRI scans of skull and cervical column showed: 1) anatomical variants of the V4 segments of the vertebral arteries (VAs); 2) atherosclerosis of the V4 segments as well as of the basilar artery; 3) degenerative changes in the cervical column; 4) hypotrophy of the pyramids in 10 cases; 5) hypotrophy of the frontoparietal cortex in 8 cases, and 6) doubtful zones of microinfarcts in the cervical cord and medulla oblongata. The electrodiagnostic tests revealed denervation and fasciculations, among other findings. Before surgery, informed consent was obtained from all patients, and the preoperative picture was recorded on videotape. The cervical cord and medulla oblongata were located through a laminectomy at the C1-C2 level [138, 140]. During surgery we made important observations: 1) anatomical variants of the V4 segments of the VAs; 2) moderate or severe atherosclerosis in both V4 segments; 3) several exsanguinated short and long circumferential arteries (arterial branches originated from the AVSAs and/or ASA); 4) hypotrophy of the anterior surface of the pyramids in 13 cases; 5) hypotrophy of small nerve roots in the row of IX, X, and XI cranial nerves, and 6) hypotrophy of the anterior roots at C5-C6 in 9 cases. The neurosurgical procedures for omental transplantation was the same that in earlier reports [138, 140, 146]. The first segment of omental tissue was placed on the anterior, lateral and posterior surface of the medulla oblongata. The second segment of omentum was placed on the laminae of the cervical verte-

brae between C2 to C4, and the third long and thin segment was placed on the cervical cord at C5-C6 in 9 cases.

Subjective and objective clinical improvement occurred beginning the first day after surgery. Almost simultaneously, all patients experienced spasticity diminished and improvement of voluntary movements in their extremities (especially in hands and feet) as well as progressive decrease of fasciculations. Likewise they experienced improvement in the bulbar symptoms in different grades. Three weeks after surgery, a 71-year-old woman with severe ALS (she presented bulbar and spinal forms) died at the hospital three weeks after surgery of a pneumonia. On the contrary, four patients have experienced a neurological improvement by 80 to 95% during the follow-up of 16 to 26 months after surgery. On admission, these patients presented moderate ALS and the onset of the disease was bulbar.

Conclusions

On 2004, I postulated that the onset of the symptoms in several NDDs are caused by ischemic neurons, continued by formation of free radicals [5], and at present, in base to a greater number of patients, we confirm this hypothesis [148]. So that, the ischemia caused by cerebral atherosclerosis, associated with vascular anomalies and/or environmental chemicals, it unchain the formation of reactive oxygen species (ROS) (superoxide anion radicals, hydroxyl radicals and peroxynitrite anion, among other free radicals) [5, 54, 148] and thus, direct or indirectly increases the formation of ROS, continuous of oxidative stress, neurodegeneration and finally, cerebral atrophy. Then, based in our results after omental transplantation, I conclude that the primary cause of NDDs are of microvascular origin, and therefore, these diseases are wrongly classified as neurodegenerative disorders.

Address correspondence to: Dr. Hernando Rafael, Bélgica 411-Bis, Colonia Portales, 03300 Mexico city, Mexico. Tel: (5255) 5532 9101; (51) 991 489 111; E-mail: hrtumi@yahoo.com

References

- [1] Ang ET, Tai YK, Lo SQ, Seet TW. Neurodegenerative diseases. Exercising toward neurogenesis and neurodegeneration. *Front Aging Neurosci* 2010; 2: 125.

Omentum for neurodegenerative diseases

- [2] Clark CN, Warren JD. A hyptic hypothesis of Alzheimer's disease. *Neurodegener Dis* 2013; 12: 165-176.
- [3] Campos I, Nogueira H, Li F, Lia F. Aging circadian rhythms and depressive disorders; A review. *Am J Neurodegener Dis* 2013; 2: 228-246.
- [4] The omentum: Research and clinical applications. In: Goldsmith HS, editor. New York: Springer-Verlag; 1990. pp. 131-145.
- [5] Rafael H. Cerebral atherosclerosis and oxidative stress in some challenging diseases. *J Neurol Sci (Turk)* 2004; 21: 343-349. www.jns.dergisi.org.
- [6] Rafael H. Aplicación clínica del epiplón en el sistema nervioso central. *Acta Med Per* 2008; 25: 176-180.
- [7] García-Gomez I, Goldsmith HS, Angulo J, Prados A, López-Hervás P, Cuevas B, Dujovny M, Cuevas P. Angiogenic capacity of human omental. *Neurol Res* 2005; 27: 807-811.
- [8] de la Torre JC, Goldsmith HS. Increased blood flow enhances axons regeneration after spinal transection. *Neurosci Lett* 1988; 94: 269-273.
- [9] Rivera F, Avila E, Carderon JL, Venezuela T, Gagne-Vogt L. Neuronal repopulation in arcuate nucleus of Hypothalamus. *Arch Neurosci (Mex)* 2009; 14: 111-115.
- [10] Ayuso-Sacido NS, Roy NS, Greenfield JP, Boockvar JA. Long-term expansion of adult human brain subventricular zone precursors. *Neurosurgery* 2008; 62: 223-231.
- [11] Shipper BM, Marra KG, Zhang W, Rubinet JP. Regional anatomic and age effects on cell function of human adipose-derived stem cells. *Ann Plastic Surgery* 2008; 60: 538-544.
- [12] Rudman D, Kutner MH, Roger CM, Lubin MF, Fleming GA, Bain RP. Impaired growth hormone secretion in adult population: Relation to age and adiposity. *J Clin Invest* 1981; 67: 1361-1369.
- [13] Rudman D, Axel G, Feller MD, Hoskote, Nagraj MD, Gregory A, et al. Effects of human growth hormone in men over 60 years old. *N Eng J Med* 1990; 323: 1-6.
- [14] Khorram O. Use of growth hormone and growth hormone secretagogues in aging: Help or harm. *Clinical Obstetric Gynecol* 2001; 44: 893-901.
- [15] Rafael H. Rejuvenation after omental transplantation on the optic chiasma and carotid bifurcation. *Case Rep Clin Pract Rev* 2006; 7: 48-51.
- [16] Rafael H. Therapeutic methods against aging. *Turkish J Geriatri* 2011; 13: 138-144. www.geriatri.dergisi.org.
- [17] Leal S, Andrade JP, Paula-Barbosa MM, Madeira MD. Arcuate nucleus of the hypothalamus: Effects of age and sex. *J Comp Neurol* 1998; 401: 65-88.
- [18] Gruenewald DA, Noai MA, Marck BT, Matsuoto AM. Age-related decrease in neuropeptide Y gene expression in the arcuate nucleus of the male rat brain is independent of testicular feedback. *Endocrinology* 1994; 134: 2383-2389.
- [19] Fernandez Galaz C, Fernandez-Agullo T, Campoy F, Arribas C, Gallargo N, Andres A. Decreased leptin uptake in hypothalamus nuclei with ageing in wistar rats. *J Endocrinol* 2001; 171: 23-32.
- [20] Rafael H. Hypothalamic ischemia and premature aging. *Med Sci Monitor* 2007; 13: LE9-10.
- [21] Rafael H. Omental transplantation for Neurodegenerative diseases. *J Aging Gerontol* 2014; 2: 24-29. <http://www.savvysciencepublisher.com/>.
- [22] Rafael H. Rejuvenation in older adults receiving oral ghrelin. *Ann Inter Med* 2009; 150: 653-654.
- [23] Flora GC, Baker AB, Loewenson RB, Klassen AC. A comparative study of cerebral atherosclerosis in males and females. *Circulation* 1968; 38: 859-869.
- [24] Milankovic Z, Vucetic R, Puzic M. Asymmetry and anomalies of the circle of Willis in fetal brain: Microsurgical study and functional remarks. *Surg Neurol* 1985; 24: 563-570.
- [25] Silva AR, Brandao RL, Moraes M. Carotid siphon geometry and variants of the circle of Willis in the origin of carotid aneurysms. *Arq Neuropsiquiat T* 2012; 70: 917-921.
- [26] Altman J. A new neurons formed in the brain of adults mammals. *Science* 1962; 135: 1127-1128.
- [27] Nunes MC, Roy NS, Keyoung HN, Goodman RR, McKhann G II, Jiang L, Kang J, Nedergaard M, Goldman SA. Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. *Nat Med* 2003; 9: 439-447.
- [28] Rafael H. Stem cells. *J Neurosurg* 2008; 108: 841-842.
- [29] Lavezzi AM, Ottaviano G, Mauri M, Maturri L. Hypoplasia of the arcuate nucleus and maternal smoking during pregnancy in sudden unexplained perinatal and infant death. *Neuropathology* 2004; 24: 284-289.
- [30] Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM. Onset symptoms in 510 patients with Huntington. *J Med Genetic* 1993; 30: 289-292.
- [31] Golberg YP, Andrew SE, Theilmann J, Kremer B, Squitieri F, Teknius H, Brown JD, Hayden MR. Familial predisposition to recurrent mutations causing Huntington's disease: genetic risk to sibs of sporadic cases. *J Med Genet* 1993; 30: 987-990.

- [32] Alonso ME, Ochoa A, Ruiz I. Enfermedad de Huntington. *Arch Neurocie (Mex)* 1998; 3: 38-46.
- [33] Gusella JF, Wexler NS, Conneally PM, Naylor S, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983; 306: 234-238.
- [34] Ross RA. Huntington's disease: a clinical review. *Orphanet J Rare Dis* 2010; 5: 40.
- [35] Gomez VI, Velit MR, Cornejo MR, Ortega GO, Marca MN, Lindo DS, et al. Late onset Huntington's disease in a peruvian cohort. *J Huntington Dis* 2013; 2: 365.
- [36] Rafael H, Mego R, Moromizato P, Buendia I. Enfermedad de Huntington y ausencia de flujo sanguíneo en las arterias recurrentes de Heubner. *Rev Mex Ateroscle* 2000; 3: 4-8
- [37] Frank S. Tetrabenazine as anti-chorea therapy in Huntington's disease: An open-label continuation study. *Huntington study group/TETRAHD investigaors. BMC Neurology* 2009; 9: 62-65.
- [38] Sramka M, Rattaj M, Vojtassak J. Transplantation of embryonal brain tissue in the treatment of Parkinsonndisease and Huntington's chorea. Presented at the 9th European Congress of Neurosurgery. Moscow USSR 1991 Jun; 279.
- [39] Cichetti F, Saporta S, Hauser RA, Parent M, Saint-Pierre M, Sanberg PR, Li XJ, Parker JR, Chu Y, Mufson EJ, Kordower JH, Freeman TB. Neural transplant in patients with Huntington's disease undergo disease-like neuronal degeneration. *Proc Natl Acad Sci U S A* 2009; 106: 12483-12488.
- [40] Bachoud-Levi AC, Gaura V, Brugières P, Lefaucheur JP, Boissé MF, Maison P, Baudic S, Ribeiro MJ, Bourdet C, Remy P, Cesaro P, Hant-raye P, Peschanski M. Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery; A long-term follow-up study. *Lancet Neurology* 2006; 5: 303-309.
- [41] Kim M, Lee ST, Chu K, Kim SU. Stem cell-based cell therapy for Huntington's disease: A review. *Neuropathology* 2008; 28: 1-9.
- [42] Zeef D, Schaper F, Vlamings R, Visser-Vandevale V, Timel Y. Deep brain stimulation in Huntington's disease: The current status *Open. Neurosurg J* 2011; 4: 7-10.
- [43] Mesulam MM, Mufson EJ, Levy AL, Wainer BH. Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal área, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol* 1983; 214: 170-197.
- [44] Rafael H. Behavioral and morphological comparison of two nonhuman primate models of Huntington's disease. *Neurosurgery* 2002; 51: 852-853.
- [45] Rafael H. Revascularization in some neurodegenerative diseases. *Medi Sci Monit* 2009; 15: LE5-6. www.medscimonit.com.
- [46] Rafael H. Transsylvian and transinsular approach. *Turkish Neurosurg* 1995; 5: 53-56.
- [47] Riggs HE, Griffiths JO. Anomalies of the circle of Willis in persons with nervous and mental disease. *Arch Neurol Psychiat (Chicago)* 1938; 39: 1353-1354.
- [48] Rafael H. Modern neurosurgery for psychiatric disorders. *Neurosurgery* 2001; 48: 1193-1194.
- [49] Gorczyca W, Morh G. Microsurgical anatomy of Heubner's recurrent artery. *Neurol Res* 1987; 9: 254-264.
- [50] Uzün L, Gürdal LE, Cakmak YO, Ozdogmus O, Cavdar S. A reminder of the anatomy of the recurrent artery of Heubner. *Cent European Neurosurgery* 2009; 70: 36-38.
- [51] Kedia S, Daisy S, Kumar K, Salunke P, Srinivasa R, Suresh M. Microsurgical anatomy of the anterior cerebral artery in Indian cadavers. *Neurol India* 2013; 61: 117-121.
- [52] Jones AL, Wood JD, Harper PS. Huntington's disease: Advances in molecular and cell biology. *J Inherited Metab Dis* 1997; 20: 125-138.
- [53] Mito R, Hayen A, McMillan J, McCusker E, Loy C. Is alcohol and tobacco abuse associated with earlier age of onset and faster disease progression in Huntington's disease. *J Huntington Dis* 2013; 2: 363.
- [54] Lannocone M, Titta F, Marra F, Gentile V. Possible role of the transglutaminases in the pathogenesis of neurodegenerative diseases. *J Aging Gerontol* 2013; 1: 18-26.
- [55] Alonso ME, Yescas P. Genetica de la enfermedad de Alzheimer. *Rev Invest Clín* 1998; 50: 155-162.
- [56] Petersen RC. Mild cognitive impairment. *New Engl J Med* 2011; 364:2227-2234.
- [57] Musiek ES, Holtzman DM. Origins of Alzheimer's disease: Reconciling cerebrospinal fluid biomarker and neuropathology data regarding the temporal sequence of amyloid-beta and tau involvement. *Curr opin Neurol* 2012; 25: 715-720.
- [58] Nandoe RS, Scheltens P, Eikelenboon F. Head trauma and Alzheimer's disease: A case report and review of the literatura. *J Alzheimer's Dis* 2002; 4: 303-308.
- [59] Van den Heuvel C, Thornton E, Vink R. Traumatic brain injury and alzheimer's disease: a review. *Prog Brain Res* 2007; 161: 303-316.
- [60] Tavares AR Jr. Psychiatric disorders in neurocysticercosis. *British J Psychiat* 1993; 163: 839.
- [61] Ramirez-Bermudez J, Higuera J, Sosa AS, Lopez-Meza E, Lopez-Meza M, Corona T. Is de-

Omentum for neurodegenerative diseases

- mentia reversible in patients with neurocysticercosis?. *J Neurol Neurosurg Psychiatr* 2005; 76: 1164-1166.
- [62] Rodriguez CL, de Andrade DC, Livramento JA, Machado LR, Abraham R, Massaroppe L. Spectrum of cognitive impairment in neurocysticercosis: Differences according to disease phase. *Neurology* 2012; 78: 861-866.
- [63] Ala TA, Doss RC, Sullivan CJ. Reversible dementia: a case of cryptococcal meningitis masquerading as Alzheimer's disease. *J Alzheimer Dis* 2004; 6: 503-508.
- [64] Srikanth S, Nagaraja AV. A prospective study of reversible dementia: frequency, causes, clinical profile and results of treatment. *Neurol India* 2005; 53: 291-4; discussion 294-6.
- [65] Rafael H. Secondary Alzheimer started by cryptococcal meningitis. *J Alzheimer Dis* 2005; 7: 99-100.
- [66] Rafael H, Mego R, Cortes R. Enfermedad de Alzheimer: Una correlación entre la etapa temprana y aterosclerosis del polígono de Willis. *Revista Climaterio (Mex)* 1999; 3: 1-7.
- [67] Rafael H, Perez-Carranco M, Valadez MT. El climaterio como factor de riesgo para la enfermedad de Alzheimer. *Revista Climaterio (Mex)* 2001; 4: 202-205.
- [68] Rafael H, Cortes R, Valadez MT. Early clinical features of Alzheimer's disease. *J Neurol Sci (Turkish)* 2003; 20: 222-227.
- [69] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007; 6: 734-746.
- [70] Rafael H, Mego R, Valadez MT. Omental transplantation on the carotid bifurcation and anterior perforated space for Alzheimer's disease. *Rev Hosp Jua Mex* 2012; 79: 25-30.
- [71] Rafael H. Onset of the symptoms in Alzheimer's disease. *Med Sci Monit* 2008; 14: LE15-16.
- [72] Rafael H. Cerebral atherosclerosis and mild Alzheimer's disease. *Stroke* 2003; 34: e106.
- [73] Jimmy A, Bladowska J, Neska M, Petryszyn K, Guzinski M, Szewczy KP. Quantitative MR evolution of atrophy, as well as perfusion and diffusion alterations within hippocampi in patients with Alzheimer's disease and mild cognitive impairment. *Med Sci Monit* 2013; 19: 86-94.
- [74] Rafael H, Mego R, Moromizato P, Espinoza M. Omental transplantation for Alzheimer's disease. *Neurol India* 2000; 48: 319-321. www.neurologyindia.com.
- [75] Rafael H, Mego R, Moromizato P, Espinoza M, Valadez M. T ransplante de epiplón para la enfermedad de Alzheimer. *Rev Climaterio (Mex)* 1999; 3: 83-89.
- [76] Rafael H, Valadez MT. Enfermedad de Alzheimer familiar: Hallazgos clínicos y tomográficos. *Rev Climaterio (Mex)* 2001; 5: 3-7.
- [77] Rafael H. Omental transposition. *Surg Neurol* 1999; 52: 539-541.
- [78] Rafael H, Lopez E, Mendez J, Rubio F. Microanastomosis vascular termino-terminal por invaginación. *Salud Pública Mex* 1986; 28: 172-175.
- [79] Rafael H. Intracranial anastomosis. *J Neurosurg* 2003; 98: 439-440.
- [80] Rafael H. Modern neurosurgery for psychiatric disorders. *Neurosurgery* 2001; 48: 1193-1194.
- [81] Rafael H, Mego R. Omental transplantation for epilepsy. *J Neurosurg* 2001; 95: 543-544.
- [82] Nigri A, Ferraro S, Dincert L, Critchley H, Bruzone M, Grazziosa M. Connectivity of the amygdala piriform, and orbitofrontal cortex during olfactory stimulation: A functional MRI study. *Neuroreport* 2013; 24: 171-175.
- [83] Sahgal A. Functions of the hippocampal system. *TINS* 1980; 3: 116-119.
- [84] Herman LH, Fernando OV, Gurdjian ES. The anterior choroidal artery: An anatomical study of its area of distribution. *Anat Record* 1966; 154: 95-102.
- [85] Drabek P. Anterior choroidal artery syndromes. *Cesk Neurol Neurochirurgica* 1991; 54: 208-211.
- [86] Rafael H. Cerebral atherosclerosis and oxidative stress in Alzheimer's disease. *J Alzheimer's Dis* 2003; 5: 479-480.
- [87] Gonzalez-Martinez JA, Bingaman WE, Toms SA, Najm IM. Neurogenesis in the postnatal human epileptic brain. *J Neurosurg* 2007; 107: 628-635.
- [88] Goldsmith HS. Omental transposition for Alzheimer's disease. *Neurol Res* 1996; 18: 103-108.
- [89] Liu XH, Zou XW. Two cases of Alzheimer's disease treated by greater omentum transplantation. Presented at the First International Congress of Omentum in CNS. Xuzhou, China: 1995 May 7-11. pp. 36.
- [90] Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer's disease: The nun study. *JAMA* 1997; 277: 813-817.
- [91] Hofman A, Ott A, Breteler MB, Bots ML, Slieter AC, Van Harskamp F, van Duijn CN, Van Broeckhoven C, Grobbee DE. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam study. *Lancet* 1997; 349: 151-154.
- [92] Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: Analysis of data from the US National Alzheimer's coordinating center. *Neurology* 2005; 64: 494-500.

Omentum for neurodegenerative diseases

- [93] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17: 427-442.
- [94] Schapira AH. Etiology of Parkinson's disease. *Neurology* 2006; 66: S10-23.
- [95] Factor SA, Weiner WJ. Prior history of head trauma in Parkinson's disease. *Mov Disorders* 1991; 6: 225-229.
- [96] Jafari S, Etminan M, Aminzadeh F, Samii A. Head injury and risk of Parkinson's disease: A systematic review and meta-analysis. *Mov Disorders* 2013; 28: 1222-1229.
- [97] Suman S, Meenakshisundaram S, Woodhouse P. Bilateral chronic subdural haematoma: A reversible cause of parkinsonism. *J Royal Soc Med* 2006; 99: 91-92.
- [98] Wiest RG, Burgunder JM, Krauss K. Chronic subdural hematoma and parkinsonian syndromes. *Acta Neurochir (Wien)* 1999; 14: 753-757.
- [99] Gralewicz S, Dyzma M. Organic solvents and the dopaminergic system. *Int J Occupat Med Environmental Health* 2005; 18: 103-113.
- [100] Pezzoli G, Cereda E. Exposure to pesticides or solvents and risk of Parkinson's disease. *Neurology* 2013; 80: 2035-2041.
- [101] Barbosa ER, Teixeira MJ, Chaves CJ, Scaff M. Parkinson's disease associated to a brain tumor: A case report. *Arq Neuropsiquiat* 1991; 49: 338-341.
- [102] Yasuhara T, Agari T, Kambara H, Ichikawa T, Korozumi K, Ono Sh. Parkinsonism related to brain tumors: A case report and review of the literatura. *Open Neurosurg* 2009; 2: 4-7.
- [103] Freed WJ, Poltorak M, Becker JB. Intracerebral adrenal medulla grafts: A review. *Experimental Neurology* 1990; 110: 139-166.
- [104] Olanow CW. Therapeutic prospects for Parkinson's disease. *Ann Neurol* 2013; 74: 339-347.
- [105] Rafael H, Malpica A, Moromizato P, Espinoza M, Ayulo V. Double autotransplant (adrenal medulla + omentum) to the putamen in Parkinson's disease. Presented at the 9th European Congress of Neurosurgery. Moscow: USSR; 1991 June 23-28. pp. 279.
- [106] Rafael H, Moromizato P, Espinoza M, Ayulo V, Gonzalez-Portillo M. Transplantation of adrenal medulla and omentum to the putamen by a transinsular approach for Parkinson's disease. *Neurosurgery* 1991; 28: 481.
- [107] Rafael H, Ayulo V. Consideraciones sobre la etiología de la enfermedad de Parkinson. *Mundo Médico (Mex)* 1990; 17: 11-17.
- [108] Rafael H. Deterioro de la microcirculación en la sustancia negra como causa de la enfermedad de Parkinson. *Rev Méd IPSS* 1995; 4: 51-56.
- [109] Rafael H. Mesencephalic ischemia and Parkinson's disease. *J Neurol Neurosurg Psychiat* 2004; 75: 511.
- [110] Rafael H, Mego R. Ablative surgery and deep brain stimulation for Parkinson's disease. *Neurosurgery* 1999; 45: 199-200.
- [111] Backlund EO, Granberg PO, Hamberger B, Knutsson E, Martensson A, Sedvall G. Transplantation of adrenal medullary to striatum in parkinsonism. First clinical trials. *J Neurosurg* 1985; 62: 169-173.
- [112] Lindvall O, Backlund EO, Farde L, Sedvall G, Freedman R, Offer B, Nobin A, Seiger A, Olson L. Transplantation in Parkinson's disease: Two cases of adrenal medullary grafts to the putamen. *Ann Neurol* 1987; 22: 457-468.
- [113] Madrazo I, Drucker-Colin R, Madrazo M, Zarate A, León V, Torres C, Reyes P. Técnica Quirúrgica del injerto autólogo de medula suprarrenal al núcleo caudado para el tratamiento de la enfermedad de Parkinson. *Gac Med Mex* 1988; 124: 365-369.
- [114] Mendez I, Dagher A, Hong M, Gaudet P, Weerasinghe S, McAlister V. Simultaneous intrastriatal and intranigral fetal dopaminergic grafts in patients with Parkinson's disease: A pilot study: Report of three cases. *J Neurosurg* 2002; 96: 589-596.
- [115] Rafael H, Moromizato P, Lara R. Surgery for Parkinson's disease. *Neurology* 1993; 43: 2154.
- [116] Rafael H, Moromizato P, Espinoza M, Lara R. Doble trasplante de tejido dopaminérgico-epiplón para la enfermedad de Parkinson. *Diagnostico (Perú)* 1996; 35: 38-41.
- [117] Rafael H. El epiplón: Trasplante al sistema nervioso. México city: Editorial Prado; 1996.
- [118] Rafael H. Omental transplantation to the insular cortex. Presented at the First International Congress of Omentum in CNS. Xuzhou, China: 1995 May 7-11. pp. 28-30.
- [119] Rafael H. Autotransplantation of human carotid body cell aggregates for treatment of Parkinson's disease. *Neurosurgery* 2004; 54: 1035-1036.
- [120] Rafael H, Moromizato O, Ayulo V. The dopamine transporter gene and Parkinson's disease in a China population. *Neurology* 1999; 52: 429-430.
- [121] Lyons KE, Pahwa R. Deep brain stimulation and essential tremor. *J Clinical Neurophysiol* 2004; 21: 2-5.
- [122] Friederike HU, Ehlen F, Krugel LK, Kühn AA, Curio G, Klostermann F, Nikulin VV. Modulation of cortical neural dynamics during thalamic deep brain stimulation in patients with essential tremor. *Neuroreport* 2013; 24: 751-756.
- [123] Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne

Omentum for neurodegenerative diseases

- F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltête D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G; EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013; 368: 610-622.
- [124] Burchiel KJ. Deep brain stimulation and depression. *J Neurosurg* 2012; 116: 313-314.
- [125] Gimble I, Guilak F. Adipose-derived adult stem cells: Isolation, characterization, and differentiation potential. *Cytotherapy* 2003; 5: 362-369.
- [126] Izadpanah R, Trygg C Patel B, Kriedt C, Dufour J, Gimble M. Biological properties of mesenchymal stem cells derived from bone marrow and adipose tissue. *J Cell Biochem* 2006; 99: 1285-1297.
- [127] Masuda T, Furue M, Matsuda T. Novel strategy for soft tissue augmentation based on transplantation of fragmented omentum and preadipocytes. *Tissue Engender* 2004; 10: 1672-1683.
- [128] Gage FH. Mammalian neural stem cells. *Science* 2000; 287: 1433-1438.
- [129] Daadi MM, Davis S, Arac A, Li Z, Maag AL, Bhatnagar R, Jiang K, Sun G, Wu JC, Steinberg GK. Human neural stem cells grafts modify microglial response and enhance axonal sprouting in neonatal hypoxic-ischemic brain injury. *Stroke* 2010; 41: 516-523.
- [130] Rafael H, David JO, Vilca AS, Aservi JL, Viera R, Medvedyev A. Transplante de epiplón para la enfermedad de Parkinson: Reporte de 3 casos. *Acta Med Per* 2013; 30: 240-245.
- [131] Dunckley T, Huentelman MJ, Craig DW, Pearson JV, Szelinger S, Joshipura K, Halperin RF, Stamper C, Jensen KR, Letizia D, Hesterlee SE, Pestronk A, Levine T, Bertorini T, Graves MC, Mozaffar T, Jackson CE, Bosch P, McVey A, Dick A, Barohn R, Lomen-Hoerth C, Rosenfeld J, O'connor DT, Zhang K, Crook R, Ryberg H, Hutton M, Katz J, Simpson EP, Mitsumoto H, Bowser R, Miller RG, Appel SH, Stephan DA. Whole-genome analysis of sporadic amyotrophic lateral sclerosis. *N Engl J Med* 2007; 357: 775-788.
- [132] Vucic S, Kiernan MC. Pathophysiology of neurodegeneration in familial amyotrophic lateral sclerosis. *Curr Molecu Med* 2009; 9: 255-272.
- [133] Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler RJ, Millul A, Benn E, Beghi E; EURALS. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatr* 2010; 81: 385-390.
- [134] Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; 344: 1688-1700.
- [135] Armon C. Smoking may be considered an established risk factor for sporadic ALS. *Neurology* 2009; 73: 1693-1698.
- [136] Gonzalez N, Escobar E, Escamilla C. Esclerosis lateral amiotrófica: Monografía. *Rev Mex Med Fis Rehabil* 2003; 15: 44-54.
- [137] Rafael H. Sporadic amyotrophic lateral sclerosis. A clinical analysis. *Rev Hosp Juárez Méx* 2010; 77: 224-227.
- [138] Rafael H, Mego R, Amezcua JP, Garcia W. Omental transplantation for amyotrophic lateral sclerosis: Case Report. *J Neurol Sci (Turkish)* 2011; 28: 101-108.
- [139] Rafael H, Ayulo V, Lucar A. Patogenia de la aterosclerosis: Base hemodinámica y factores de riesgo. *Rev Climaterio (Mex)* 2003; 6: 125-128.
- [140] Rafael H, David JO, Vilca AS, Aservi JL, Sánchez MP, Medvedyev A, Viera R, Lazo EM, River H, Coronado DE. Esclerosis lateral amiotrófica: Experiencia quirúrgica en 13 pacientes. *Acta Med Per* 2013; 30: 79-85.
- [141] Sidoti C, Agrillo CU. Chronic cortical stimulation for amyotrophic lateral sclerosis: A report of four consecutive operated cases after a 2-year follow-up: Technical case report. *Neurosurgery* 2006; 58: E384; discussion E384.
- [142] Martinez H, Gonzalez-Garza M, Moreno-Cuevas J, Caro E, Gutierrez-Jimenez E, Segura J. Stem-cell transplantation into the frontal motor cortex in amyotrophic lateral sclerosis patients. *Cytotherapy* 2009; 11: 26-34.
- [143] Deda H, Inci MC, Kürekçi AE, Sav A, Kayihan K, Özgün E, Ustünsoy GE, Kocabay S. Treatment of amyotrophic lateral sclerosis by autologous bone marrow-derived hematopoietic stem cells transplantation: a 1-year follow-up. *Cytotherapy* 2009; 11: 18-25.
- [144] Rafael H, Moromizato P, Espinoza M, Malpica A. Transplante de epiplón al cerebelo en pacientes con trombosis de la arteria vertebral. *Diagnostico (Peru)* 1992; 30: 23-26.
- [145] Rafael H. Revascularization of the brainstem and cerebellum. *Neurosurgery* 2010; 67: ES21.
- [146] Rafael H, Mego R, Amezcua JP, Garcia W. Transplante de epiplón para la neuralgia occipital primaria. *Acta Med Per* 2009; 26: 92-94.
- [147] Rafael H. Brainstem ischemia. *J Neurosurgery Spine* 2009; 11: 88-90.
- [148] Rafael H. Cerebral atherosclerosis causes neurodegenerative diseases. *Med Sci Monit* 2010; 16: LE1-2. www.medscimonit.com.