Hypothalamic Revascularization and Rejuvenation

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Abstract: *Background*: Since 1990 and to date, four therapeutic methods have been used against aging. All of them, to increase the plasma growth hormone levels.

Material and Method: We choose 38 patients to analyse the postoperative rejuvenation. Previously, all of them have been received omental transplantation on the optic chiasma, the carotid bifurcation and the anterior perforated space. Patients with stroke in 14 cases, Alzheimer´s disease (AD) in 23 and Huntington´s disease (HD) in 1. The clinical data of rejuvenation were obtained by observation, videotape and photography.

Results: Neurological improvement in patients with stroke, AD and HD were better during the first weeks after surgery than in the following months or years. Besides this, between 1 to 4 months after surgery, 32 patients (84.21%) showed rejuvenation and in the rest, there were not changes. These 6 last patients presented dilation of the third ventricle.

Conclusions: These results indicate that the primary cause of aging is of ischemic origin, in the arcuate nucleus of the hypothalamus. Because, in contrast to this, its revascularization by means of omental tissue produce rejuvenation. Therefore, our surgical method improve the function of the residual arcuate nucleus and adjacent zones.

Keywords: Aging, Arcuate nucleus, Hypothalamic ischemia, Omental transplantation.

INTRODUCTION

Since 1981, we known that the aging process is caused by a deficiency of growth hormone (GH) [1] and 9 years later on, the same authors reported rejuvenation in persons over 60 years of age after the subcutaneous administration of biosynthetic human GH [2]. Since then, four therapeutic methods have been used against aging [3-7]: 1) treatment with GH, 2) treatment with growth hormone-releasing hormone (GHRH), 3) treatment with GH secretagogues (GHS), and hypothalamic revascularization.

We present to a group of patients whom received omental transplantation on the carotid crotch to improve cerebrovascular sequelae [8], Alzheimer´s disease (AD) [9, 10] and Huntington´s disease (HD) [11, 12], of 85 patients, we choose only 38 cases to analyse an unexpected finding: rejuvenation.

MATERIAL AND METHOD

Clinical Cases

Between May 1997 and December 2011, we have placed omental tissue on the carotid bifurcation into 60 patients with stroke caused by essential arterial hypertension (EAH) and type 2 diabetes mellitus (DM) (ie., EAH plus type 2 DM in 4 cases) [8, 13, 14], sporadic AD in 23 patientes (mild AD in 5 cases and moderate AD in 18) [9, 10, 15]. and two patients with HD (familial HD, 1 case and sporadic HD in 1) [11, 12, 16]. Preoperative computed tomographic (CT) and magnetic resonance imaging (MRI) scans revealed atherosclerosis in the supraclinoid carotids and/or circle of Willis in all patients with stroke [8], AD (Figure **1**) and advanced HD (Figure **2A**). In all them, the preoperative clinical picture was recorded on videotape and later on, the postoperative findings were also documented on 2 to 5 videotape.

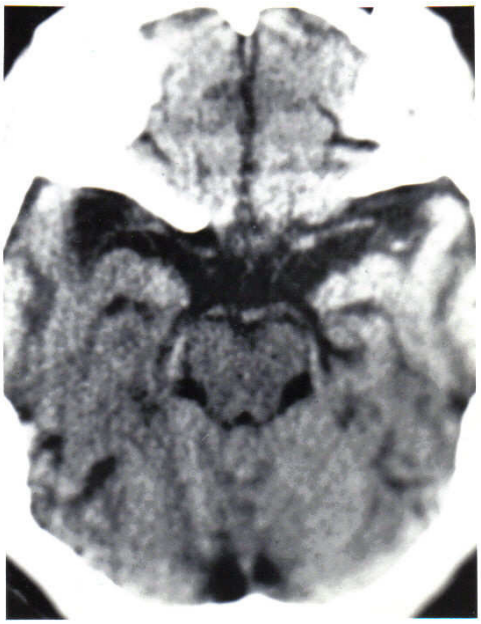

Figure 1: CT scan without contrast showing atherosclerosis in the supraclinoid carotids and the middle and posterior cerebral arteries in a 53-year-old woman with moderate AD.

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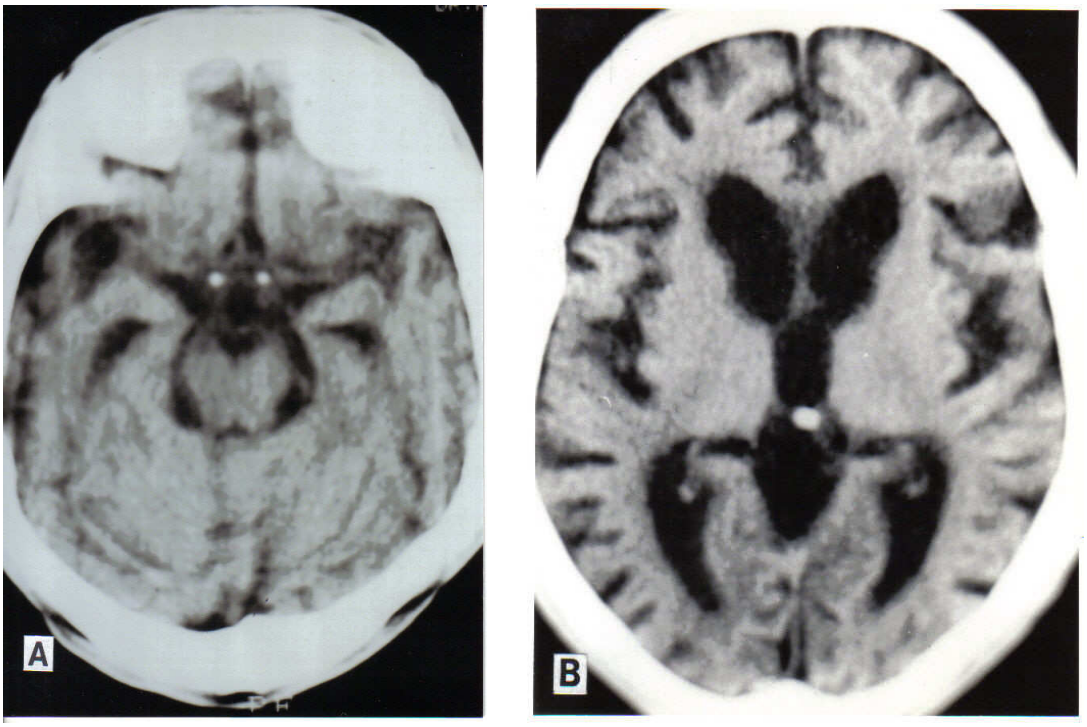

Figure 2: A. CT scan without contrast showing atherosclerosis of the circle of Willis and proximal segments of the anterior and middle cerebral arteries in a 35-year-old man with familial HD.

B.CT scan without contrast showing severe cerebral atrophy, dilatation of the III ventricle and severe atrophy in the head of caudate nuclei, in a 35 year-old man with familial HD.

However, of the 85 patients operated, here we report only 38 patients (stroke in 14 cases, AD in 23, and HD in 1) whom have kept communication with us. The age of these patients fluctuated between 53 and 82 years, except the patient with familial HD of 35 years of age (Figure **2A** and **2B**). Thirty patients were women and 8 men.

Every one of them was operated to improve the neurological sequelae [8, 17], sporadic AD [10, 18] and familial HD [11, 12, 16]. That is, these 38 patients were operated to improve the neurological disease. For these reasons, the preoperative serum GH and insulin-like growth factor-I (IGF-I, also known as somatomedin C) levels were not measured, because no patient was operated specifically to rejuvenate. The rejuvenation was a finding after omental transplantation, which was documented by videotape, photography, clinical observation and in some cases by telephonic information.

Operation

Basically the same neurosurgical technique was performed in all of them [8, 11, 17]. Briefly, a fronto-temporal craniotomy and laparotomy were performed simultaneously by neurosurgeon and general-surgery teams, respectively. In abdomen, by means of laparotomy, a segment of omentum was obtained, which contained vascular elements of good caliber. In skull, through a pterional-transsylvian approach we localed the carotid bifurcation. Here, with help of the operating microscope we identified the C4 segments of the internal carotid arteries (ICAs) and its collateral branches:ophthalmic, anterior perforating, anterior choroidal and posterior communicating arteries.During surgery we made four important observations: 1) anatomical variants of the terminal and collateral branches of the C4 segments of the ICAs, 2) moderate or severe atherosclerosis, 3) variable number of exsanguinated and collapsed anterior perforating arteries and 4) some perforating arteries with residual blood flow centripetal to the origin of the vessels.

Previous end-to-end anastomoses by invagination between the superficial temporal vessels and the gastroepiploic vessels of the omentum, an omental segment was placed on the optic chiasma, and other segment on the carotid bifurcation and anterior perforated space (APS). Levels with the right (11 cases) or left sylvian fissure, the omental segment was secured to the pia-arachnoid. The vascular pedicle with anastomoses pierced the duramater and a burr hole.After placed the bone, the wounded scalp was closed.

RESULTS

Neurological improvement in various aspects of their motor, sensory, bladder and speech functions was observed in all patients with stroke [8, 17]. In 5 mild AD patients there were complete reversal of symptoms since the first days after the operation; meanwhile in 18 patients with moderate AD, we observed only, clinical improvement in different degrees [10]. The patient with familial HD also presented improvement in his facial expression, short-term memory and the muscular rigidity diminished. Up to three months after surgery he could eat and walk with or without familiar assistance [11, 12]. In all patients, we oberved that neurological improvement was better during the first weeks after surgery than in the following months o years.

In 32 of 38 patients operated, we observed different degrees of rejuvenation and in the 6 remainder, the changes were uncertain or null, ie., there were rejuvenation on 84.21% of cases. The scarce or absence of rejuvenation on the 6 patients, was related with dilation of the third ventricle (Figure **2B**). Between 1 to 4 months after surgery, the patients presented wrinkles decreased in the face (32 cases), better skin texture (32 cases), good elasticity of skin (28 cases), new hair growth black-coloured (27 cases), increase of muscular mass in thighs (24 cases), increased muscle strength (23 cases), decreased visceral obesity (22 cases), improvement of visual acuity and field (20 cases) and recent memory improvement (20 cases), among other changes. Likewise, 6 of 8 men presented increase of libido/sexual potency. A 82-year-old man reported previously [6, 7] is a typical example of rejuvenation after omental transplantation. After surgery, no patient received GHRH, GH or GHS, not even testosterone.

DISCUSSION

Up to now, all researchers agree that the aging process is caused by a decline of GH levels in our bodies, and on practically every persons after 30 years, there is a direct correlation between decreasing GH levels and the effects of aging [2, 4, 7].

Based on previous observations [6, 7, 19], we have postulated that the aging process is a disease, caused by progressive ischemia in the arcuate nucleus of the hypothalamus and adjacent areas. That is, in the producing hypothalamic nuclei (lowermost portion of the ventromedial nuclei, arcuate nucleus and both tuber cinereum) of GHRH. The arcuate nucleus (Figure **3**), main producing hypothalamic nucleus of GHRH, also is constituted by small cells such as dopamine (A12 cell group), Luteinizing hormone-releasing hormone (LHRH), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), and proopiomelanocortin (POMC) neurons; as well as ependymal cells and tanacytes [20-26]. The unmyelinated axons of dopamine, GHRH, LHRH, and VIP neurons terminate directly upon the perivascular space of the portal capillary plexus in the median eminence; meanwhile the axons of the NPY and POMC neurons terminate in the ventromedial, dorsomedial and paraventricular nuclei, as well as in the lateral hypothalamic area (LHA) [20, 24, 27-30]. The arcuate nucleus receive excitatory impulses from the hippocampus through the postcommissural fibers of the fornix, and monoaminergic and cholinergic axons from the brainstem [22, 23, 31]. So that, the raphe nuclei through the ascending serotoninergic pathways provoke a pulsatile GHRH secretion during the early phase of sleep [22, 31].

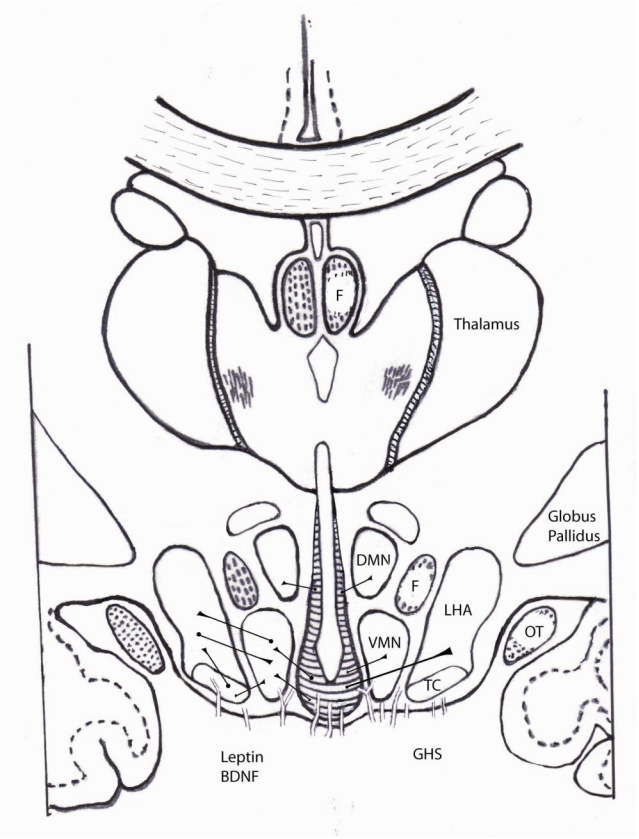

Figure 3: Illustration of a coronal section through the arcuate nucleus, and ventromedial (VMN) and dorsomedial (DMN) nuclei. Fornix (F). Lateral hypothalamic area (LHA). Tuber cinereum (TC). Optic tract (OT). Brain-derived neurotrophic factor (BDNF) and growth hormone secretagogues (GHS).

The producing hypothalamic nuclei of GHRH receive its blood supply through small arteries and arterioles originated from three large perforating

arteries and from the circuminfundibular plexus [6, 32, 33]: 1) superior hypophyseal arteries originated from the ophthalmic segment of the supraclinoid carotids (C4 segments of the ICAs), 2) infundibular or premammillary arteries arose from the posterior communicating arteries (PCoAs) and 3) some perforating branches originated directly from the communicating segment of the supraclinoid carotids. In other words, the basal and medial portions of the hypothalamus are vascularized essentially by small arteries (range 0.07 to 0.40 mm of caliber) and arterioles originated from the circuminfundibular plexus. Therefore, the arcuate nucleus is very vulnerable to ischemic lesion (Figure **3**).

Between 25 to 30 years of age, the cerebral blood flow (CBF) decline progressively to means values of adults (50 to 55 ml/100 gr/min) [34, 35]; and in general, starting from 50 years, the CBF and glucose consumption are reduced still more. Deterioration circulatory that coincides with the appearance of atheromatous plaques in the supraclinoid carotids [36, 37]. For these reasons, we believe that atheromatous plaques located at the mouths of the superior hypophyseal, infundibular and other perforating arteries are responsibles of progressive ischemia in the arcuate nucleus, ventromedial nuclei, both tuber cinereum and adenohypophysis. However, it is very possible that the degree of ischemic lesion is also related with anatomical variants of these collateral arteries originated from the supraclinoid carotids [33, 37, 38].

Therefore, in base to above-mentioned observations and postoperative findings in our 32 patients, my colleagues and I believe that the aging process was caused by progressive ischemia in the median eminence and producing arcuate nucleus of GHRH and LHRH, among others.Thus, the synthesis and secretion of GHRH and LHRH decline with age and the degree of atherosclerosis.The GHRH causing of decreasing GH levels and effects of aging, meanwhile the second, with decreasing follicle stimulating homone (FSH) and luteinizing hormone (LH) levels and sexual dysfunction in older men and women [3, 6]. Likewise, in the arcuate nucleus there is progressive loss of NPY and POMC neurons (with orexigenic action) [20, 26, 39] and therefore, a lack of response to the inhibitory action of leptin and brain-derived neurotrophic factor (BDNF), as well as to the excitatory action of GHS (especially of the ghrelin) on the NPY and GHRH neurons [19, 29, 30, 40]. Moreover, clinical evidences indicate that the extension of this ischemic injury in the ventromedial nuclei (satiety center) can cause increase of appetite, obesity and type 2 DM [13, 24, 40, 41]; in the posterior hypothalamic nuclei, EAH [8, 18], and in subcommissural regions (constituted by cholinergic and neuropeptidic nuclei) and medial temporal lobes (implicated in the recent memory), AD [9, 10, 15, 18]. That is, ischemic lesion in the arcuate nucleus causes aging and years later, in the subcommissural regions causes AD; because, on the contrary, an omental transplantation on the carotid bifurcation and APS produce rejuvenation and moreover, it can cure (degree mild) or improve (degree moderate) AD [10].

So therefore, since 1990 and to date, four therapeutic methods can be used against aging: 1) treatment with GH; 2) treatment with GHRH; 3) treatment with GHS (ghrelin and synthetic GHS), and 4) hypotalamic revascularization with omental tissue. The three first are palliative or replacement methods, because they increase only the serum GH concentration following oral or subcutaneous administration; whereas the fourth is a reconstructive or physiological method, because through the omental tissue, the cells of the residual arcuate nucleus receives an increase in blood flow, oxygen, neurotransmitters, neurotrophic factors, adipocytokines and omental stem cells [17, 42-45]. Thus, the function of neurons (especially of GHRH and LHRH neurons) in the residual arcuate nucleus in ischemia and ischemic penumbra can improve since the first days after surgery and later on, because of neuronal regeneration and neurogenesis [42, 46, 47].

The rejuvenation observed in the 32 patients confirm our previous studies [6, 7, 19] and it reaffirm that aging is a disease [7, 19]. In addition to this, the study incorporate that the rejuvenation in elderly people with dilation of the third ventricle my be scarce or null; due, probably, to the absence of GHRH neurons in the producing hypothalamic nuclei of this hormone. Moreover, we believe that the little effectiveness of the treatment with GHS in older persons [3, 19] is due to the lack of entrance of GHS in the arcuate nucleus and adjacent nuclei, because several perforating arteries are exsanguines.Likewise, inflammatory lesions in the chiasmatic cistern are also recognized as causes of GH deficiency [22], and is probable that the perforation of the floor of the third ventricle (third ventriculostomy) for patients with hydrocephalus, it may also damage to the arcuate nucleus. Finally, we want to comment that the use of antioxidant products against aging, they have only the purpose of avoid oxidative stress in the cells of the body [18], but not provoke revascularization in the hypothalamus.

CONCLUSIONS

These observations indicate that the primary cause of the aging process is of ischemic origin, initiated in the arcuate nucleus of the hypothalamus. Because, in contrast to this, its revascularization by means of omental tissue provoke rejuvenation, and the degree of improvement seems to be related with the amount of residual neurons in the producing hypothalamic nuclei of GHRH, as well as in the adenohypophysis.

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