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Omental transplantation on the carotid bifurcation and anterior perforated space for Alzheimer's disease

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RESUMEN

Antecedentes. Cada vez son más las evidencias de que la aterosclerosis cerebral se asocia con un riesgo aumentado para la enfermedad de Alzheimer (EA). **Material y métodos.** Se atendieron 152 pacientes con EA (mujeres 124 casos y hombres 28), 94% fueron casos no genéticos. En todos los pacientes el grado inicial se caracterizó por 1) Pérdida progresiva de la memoria reciente y 2) Cambios en el comportamiento y personalidad; ambos como síntomas iniciales. Los estudios de tomografía computada y de resonancia magnética revelaron: 1) Parénquima cerebral normal o con leve atrofia y 2) Aterosclerosis en las carótidas supraclinoideas. Veintitrés pacientes (EA moderado en 18 casos y EA inicial en cinco) recibieron transplante de epiplón sobre la bifurcación carotídea y zonas circundantes. Durante la cirugía se encontró aterosclerosis moderada o severa en las carótidas supraclinoideas, algunas arterias perforantes anteriores exsangües y otros ramos con flujo sanguíneo residual centripetal al sitio de origen. **Resultados.** Los síntomas en todos los pacientes con EA inicial fueron revertidos después de los primeros días de la operación; mientras que en los pacientes con EA moderado solamente hubo mejoría neurológica. **Conclusiones.** Estos resultados indican que el agente etiológico de la EA es de origen isquémico iniciado en el territorio intraparenquimatoso de las arterias coroideas anteriores y perforantes anteriores causado por aterosclerosis.

Palabras clave: *Aterosclerosis cerebral, lóbulo temporal medial, regiones subcomisurales, enfermedad de Alzheimer, trasplante de epiplón.*

ABSTRACT

Background. Every time is increasing evidences that cerebral atherosclerosis is associated with an increased risk for Alzheimer's disease (AD). **Material and methods.** We attended to 152 patients with AD (women, 124 cases and men 28), in which the 94% were non-genetic cases. In all patients, the mild degree was characterized by 1) Progressive loss of recent memory and 2) Behavioral and personality changes, both data as initial symptoms. Computerized tomography scans and magnetic resonance image revealed 1) Normal cerebral parenchyma or slight cerebral atrophy, and 2) Atherosclerosis at the supraclinoid carotids. Twenty-three patients (moderate AD in 18 cases and mild AD in 5) received omental transplantation on the carotid bifurcation and surrounding zones. During surgery we found moderate or severe atherosclerosis in the supraclinoid carotids; some exsanguinated anterior perforating arteries, and other branches with residual blood flow centripetal to the site of origin. **Results.** In all mild AD patients there were complete reversal of symptoms since the first days after surgery; meanwhile in moderate AD patients only there were neurological improvement. **Conclusions**. These results indicate that the etiologic agent of AD is of ischemic origin initiated in the intraparenchymal territory of the anterior choroidal and anterior perforating arteries caused by atherosclerosis.

Key words: *Cerebral athrosclerosis, medial temporal lobes, subcommissural regions, Alzheimer's disease, omental transplantation.*

INTRODUCTION

Previous studies have revealed that cerebral atherosclerosis,[1] the free radicals generation[2] and the oxidative stress,[3] are early events in the pathophysiology of Alzheimer's disease(AD), especially when occurs in the medial temporal lobes and subcommissural regions.[4,5] For these reasons, on March 1993, Goldsmith[6] placed for the first time omentum over the right parieto-occipital cortex to a moderate AD patient. The patient improved for a year following surgery but after that time slowly began to decline neurologically. Five years later, based on anatomic data[7] and autopsy findings,[1] we transplanted omental tissue on the optic chiasma and anterior perforated space (APS) to a 75-year-old woman with mild AD.[8] She remained symptom-free since the first days after surgery. Since then and to date,we use the same surgical technique in mild AD or moderate AD patients.

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Table 1. Alzheimer's disease: clinical variety and age of onset.

Cases (%)	Clinical variety	Onset of the symptoms (age in years) Range	Average
118 (77.64)	Sporadic	45-85	65.8
25 (16.44)	Uncertain	47-83	67.2
9 (5.92)	Familial	34-40	36.2

MATERIAL AND METHODS

Patients

Unlike the clinical criteria established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) for the diagnosis of AD;[9,10] since 1999, we used a viewpoint different.[4,11] First, the participants were divided into three groups with regard to its clinical variety or form (Table 1):

- **Sporadic cases**. None of the patients had evidence of familial history of AD;
- **Uncertain cases**. This group was chosen like that, because the mean age at onset of this disease was similar to the sporadic cases and also, every patient had only 1 to 3 close relatives with the same disease, and
- **Familial cases**. The patients had between 4 to 9 close relatives with AD and, in whom the disease began between the ages of 34 to 40 years.

There were 124 women (81.58%) and 28 men (18.42%). Second, as the clinical findings appeared of manner sequential and progressive, the clinical stage was divided in mild, moderate and advanced degree.[4,11]

So then, in base to these observations, between January 1998 and January 2011, we have attended to 152 patients with AD: mild AD was seen in 42 cases, moderate in 83, and advanced in 27. We put special attention to the transition zone between "normal aging" and the onset of the symptoms. In the manner of previous studies,[4,11,12] a prospective and retrospective analysis was performed of the early stage (mild degree) in the 152 participants, which was characterized by:

- Progressive loss of recent memory in 72.37% (typical course, because it was the first symptom of AD), and
- Behavioral and personality changes 27.63% (atypical course); both data as initial symptoms, and with less frequency associated with
- Olfactory and gustatory (23.68%) or visual (9.86%) deficits, 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 at sea level or following hyperbaric oxygenation therapy alternated with those of worsening symptoms), and progressive.

Likewise in all patients with mild degree, computerized tomography (CT) scans and/or magnetic resonance image (MRI) showed two important findings. First, normal cerebral parenchyma or slight cerebral atrophy that was normal for the age (Figure 1), and Second, atherosclerosis at the supraclinoid carotid arteries (C4 segments), circle of Willis and at the basilar artery. On the contrary, neuropsychological tests in 106 patients with mild AD revealed clinical

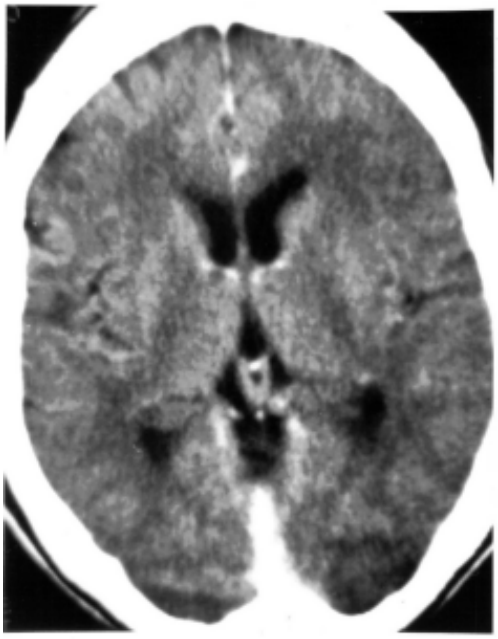

Figure 1. *Preoperative CT scan with contrast, showing slight dilatation in the left frontal horn of the lateral ventricles, in a 75-year-old woman with mild AD.*

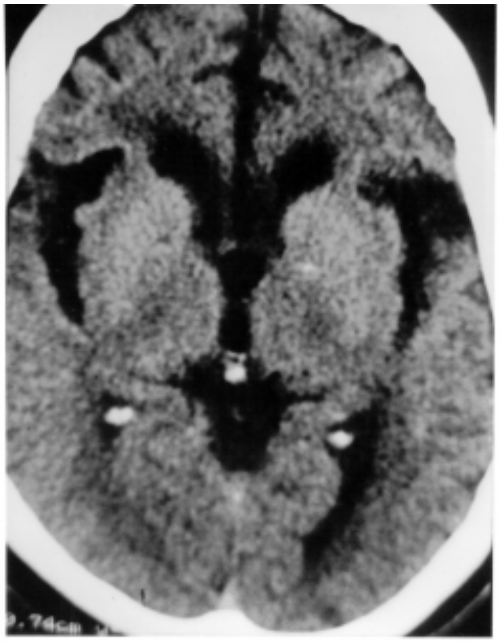

Figure 2. *CT scan without contrast, showing moderate diffuse cortical atrophy and moderate dilatation of the ventricular system, in a 63-year-old woman with moderate AD.*

data of dementia. Therefore, the diagnosis of mild AD was clinical and by contrast, auxiliary studies as CT scans, MRI, single photon emission computed tomography (SPECT) or positron emission tomography (PET) proportioned little aid.[4,5,11,12]

In addition to the clinical data of mild AD, the moderate AD was characterized by:[4,11]

- Slight or moderate impairment of higher cortical functions (aphasia, apraxia and agnosia),
- Posture and/or gait disturbances,
- Motor and sensory impairment,
- The diagnosis of dementia is obvious, and
- Slight or moderate cerebral atrophy (Figure 2) demonstrated by CT scans and/or MRI.

Our first patient operated (May 1998) was a 75-year-old woman with a 10-year history of type 2 diabetes mellitus (DM) and two years later, she developed mild AD.[4,8,13] Likewise, seven of 18 patients operated with moderate AD had previous complications: essential arterial hypertension(EAH) in 5 cases and type 2 DM in 2.

Surgery

Between May 1998 and to date, we have transplanted omental tissue into 18 patients with moderate AD and in 5 with mild AD, in accordance with a surgical technique previously published by us.[8,13] Briefly, a frontotemporal craniotomy and laparotomy were performed simultaneously by neurosurgeon and general-surgery teams respectively. Through a left or right pterional-transsylvian approach, we located the carotid bifurcation. Here during surgery we made four important observations

- Moderate or severe atherosclerosis in the C4 segments and its branches,
- Anatomical variants in the anterior choroidal and anterior perforating arteries,
- A variable number of exsanguinated and collapsed anterior perforating arteries, and
- Some perforating branches with residual blood flow centripetal to the origin of these vessels.

Besides these findings, into the 18 moderate AD patients we found cerebral atrophy within the surgical zone. Previous end-to-end anastomoses by invagination between the superficial temporal vessels and the gastroepiploic vessels of the omentum, the omental graft was placed on the optic chiasma, carotid bifurcation and APS.

RESULTS

Subjective and objective improvement occurred beginning with the first or second day after surgery in all mild AD patients and they remained symptom-free starting from two weeks later. At present, several years later, their quality of life in 4 patients is good and without medical treatment for AD. Moreover, the 5 patients experienced some changes of rejuvenation revealed in the hair, skin testure, increased muscle strength, body fat loss, normalization of the taste and smell, and improvement of visual function. The first patient had a follow-up of 6 years (Figure 3). She died suddenly at her home of a myocardial infarction.[13]

In all 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 one and other patient. For example, a 74-year-old man with moderate AD reported previously[14] and with severe atrophy in both of them temporal lobes, he has experienced only very little improvement in short-term memory. Meanwhile a 53-year-old woman with the same degree of disease,[4,15] and moderate cortical atrophy and moderate dilatation of the ventricular system (Figure 2), at present she present a neurological improvement about 85% in relation to preoperative clinical data.[8,15]

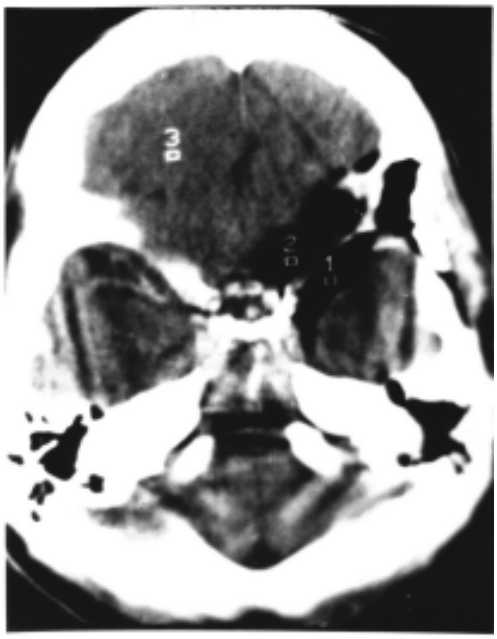

Figure 3. *Postoperative CT scan with contrast obtained 3 months after surgery, showing the presence of omental tissue over the left sphenoid ridge, optic chiasma, carotid bifurcation and anterior perforated space, in the same patient of figure 1.*

Moreover, in 13 of 18 moderate AD patients operated, we observed some changes of rejuvenation, but less evident than in mild AD patients. On the other hand, EAH into 5 patients was normalized and without antihypertensive medication. Likewise, the hyperglycemias in 3 patient with type 2 DM (mild AD in 1 case and moderate AD in 2) were normalized.

DISCUSSION

There is no doubt that in the manner of parkinsonism,[16] there are two types of Alzheimer: primary Alzheimer or AD, and secondary Alzheimer caused by previous atherosclerosis in the large and small vessels of the chiasmatic cistern associated with hemorrhage due to traumatic brain injury,[17] cryptococcal meningitis[18] and neurocysticercosis,[19] among other causes. The clinical cases attended and operated by us, they belong to AD.

We believe that the complete reversal of symptoms in the mild AD patients was due to revascularization of neurons in ischemia and ischemic penumbra in the intraparenchymal territory of the anterior choroidal and anterior perforating arteries. Thus, the optic chiasma, the hypothalamus, the olfactory striae, the optic tracts, the subcommissural regions (constituted by cholinergic and neuropeptidic nuclei as well as their fiber bundles, especially medial forebrain bundles),[8,14,20] and the medial temporal lobes (hippocampal formation, entorhinal region and the amygdaloid body), all of them received an increase in blood flow, oxygen, neurotransmitters, neurotrophic factors, cytokines and omental stem cells from the omental tissue.[21,22] For these reasons, since January 2000, we have postulated that mild AD can be inured.[5,8,11,12] Because the primary cause of this disease is of ischemic origin due to the presence of atherosclerotic plaques located at the mouths of the terminal and collateral (anterior choroidal and anterior perforating arteries, among ithers) branches from the supraclinoid carotids. Therefore, AD is wrongly classified as a neurodegenerative disease.[3,5]

Thus, by means of our surgical modality we improved the function of cell bodies and dendrites of cholinergic and neuropeptidic neurons in the subcommissural regions, as well as of neurons in the medial temporal lobes.[7,14] In other words, we revert (functional recovery) the neuronal deterioration in these brain zones through the omentum. Being as the omental tissue is the best tissue for developing vascular connections with underlying and adjacent nervous tissue since the first hours of the omental transplantation.[22] Thereby, our surgical method is completely different to palliative methods such as omental transposition[6,23] and pharmacologic options, because both procedures acts in the axonic terminals and synaptic cleft of cholinergic axons in the cerebral cortex and by contrast, our surgical technique acts in the cholinergic and neuropeptidic nuclei.[7,14]

On the other hand, we think that the neurological improvement observed in moderate AD patients was also due to revascularization of the residual nervous tissue (areas in ischemia, ischemic penumbra, and local or diffuse atrophy), especially in diencephalic structures and surrounding zones. So therefore, our results indicate that the clinical improvement is related essentially with the degree of morphological recovery in the subcommissural regions[7,14] and medial temporal lobes ,and secondly, because of neuronal regeneration and neurogenesis.[21 24] That is, the omental tissue placed on the carotid bifurcation and APS has a key rol in the treatment of mild or moderate AD.

Finally, we wish to comment about aging, type 2 DM and EAH. In previous publications we have informed that these three challenging diseases are caused by progressive ischemia in the hypothalamus due to atherosclerosis in the supraclinoid carotids and circle of Willis. Our results indicate that 1). The aging process (initiated between 25 to 30 years of age) is caused by progressive ischemia in the producing hypothalamic nuclei (lower most portion of the ventromedial nuclei, arcuate nucleus and tuber cinereum) of

growth hormone-releasing hormone (GHRH).[25] 2) Type 2 DM is caused by ischemia in the anterior hypothalamic nuclei and later on, in endocrine pancreas,[13,26] and 3) EAH caused essentially by ischemia in the posterior hypothalamic nuclei.[3] Both of them (type 2 DM and EAH) diseases are initiated generally starting from 30 years of age. Because, in contrast to this, the revascularization by means of omental tissue produces rejuvenation, cause decrease or normalization in hyperglycemia and it can normalize EAH. Therefore, the aging process is a disease initiated in the arcute nucleus of the hypothalamus, and AD is caused by ischemia in the subcommissural regions and medial temporal lobes. Thereby, the administration of human growth hormone in AD patients is not effective.

CONCLUSIONS

The onset of the symptoms in all AD patients is characterized by 1) progressive loss of recent memory (72.37%) and 2) Behavioral and personality changes, both data as initial symptoms, and with less frequency associated with olfactory, gustatory or visual deficits. CT scans and/or MRI showed normal cerebral parenchyma or slight cerebral atrophy, and also, atherosclerosis in supraclinoid carotids. Twenty-three patients (moderate AD in 18 cases and mild AD in 5) received omental transplantation on the carotid bifurcation and surrounding zones. In all patients with mild AD, we observed complete reversal of symptoms since the first days after operation, whilst moderate AD patients only showed neurological improvement.

These clinical results indicate that the etiologic agent of AD is of ischemic origin initiated in the intraparenchymal territory of the anterior choroidal and/or anterior perforating arteries, secondary to atherosclerotic plaques located at the site of origin of these collateral branches from the supraclinoid carotids.

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