Omental Transplantation For Infantile Cerebral Palsy
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Summary
Background: Infantile cerebral palsy (ICP) is currently one of the major diseases that cause paralysis and mental retardation in children. The stem cell treatment is a promising alternative for this disease.

Material and method: Twenty-eight patients with ICP and epilepsy (12 cases) since 4.5 to 24 years received omental transplantation on the carotid bifurcation, anterior perforated space (APS), optic chiasm, and the temporal lobes. During surgery we found: 1) small and thin omentum in 13 cases, 2) adhesive arachnoiditis in the chiasmatic cistern and surrounding areas in 18 cases, 3) ischemic microinfarcts and atrophy in the surgical area; 4) vascular anomalies in the anterior perforating arteries; 5) several collapsed and exsanguinated perforating arteries, and 6) arachnoid cyst in 3 cases. Of all patients, thirteen cases received only, omentum on the APS, because the omentum was small.

Results: Neurological improvement occurred since the first days after surgery in 21 patients. The epileptic seizures were reduced or aborted. Currently, 10 to 26 months after the operation, the patients have improved in different degrees. Likewise, the clinical data in 10 patients with minimal brain dysfunction were reversed.

Conclusions: These results indicate that omental transplantation against ICP is effective. Because the omentum provoke revascularization and provide mesenchymal stem cells to the injured area, Moreover, the omentum favors the proliferation and migration of neural stem cells from the subventricular zone of the adult human brain.

Key words: Cerebral palsy, Cerebral atrophy, Adhesive arachnoiditis, ischemic microinfarction, stem cells

Infantil Serebral Felç için Omental Transplantasyon

Özet
Giriş ve Amaç: İnfantil serebral felç (ICP) günümüzde çocuklarda mental retardasyon ve felce neden ana hastalıklardan biridir. Bu hastalık için kök hücre tedavisi umit verici bir alternatifdir.

Gereç ve Yöntem: ICP (28 hasta) ve epilepsi (12 hasta) olgularına 4,5 ila 24 yıllık bir periodda karotid bifurkasyon, anterior perforan alan (APS), optik kiazma, temporal loblar üzerine omental transplantation uygulandi. Cerrahi sırasında 1) 13 olguda küçük veince omentum, 2) 18 olguda kiazmatik sistern ve çevresinde adeziv araknoiditis, 3) cerrahi alanda ishemik mikroinfarktlar ve atrofi, 4) anterior perforan arterlerde vasküler anomaliler, 5) bir çok sayıda kollabe olan ya da kapanan perforan arterler, 6) 3 olguda araknoid kist saptandi. Tüm hastalar, sadece onüç olgu, omentum küçük olduğundan APS üzerine uygulandi.

INTRODUCTION

The minimal brain dysfunction (MBD) and infantile cerebral palsy (ICP) are two neurological diseases caused by the same etiologic agents. In the first, microscopic lesions are located in the medial temporal lobe and orbitofrontal cortex\(^\text{(12,15)}\), whereas in the second, gross lesions involving the cerebral cortex, diencephalon, cerebellum or a combination of all them. In both neurological disorders, ischemic, hypoxic, infectious and toxic agents, among others; all of them damage to the fetus during pregnancy, childbirth or in the postnatal period\(^\text{(7,12,30)}\).

To date, the treatment of ICP is multidisciplinary, which highlights the rehabilitative; that is, that the ICP is not curable, but can be improved by transplantation of embryonic nervous tissue\(^\text{(15,29)}\), fetal\(^\text{(2,14)}\), omental transplantation\(^\text{(21)}\) and recently, through stem cells\(^\text{(3,8,27)}\). For this reason and based on our wide experience with omental transplantation on the nervous system, we decided to transplant the same tissue to a group of patients with ICP.

MATERIAL AND METHODS

Clinical Cases: Between August 2011 and August 2013 , we attended 115 patients with ICP, corresponding to 67 men and 48 women, whose ages ranged from 2.3 years to 24 years. All of them had clinic diagnosis of ICP, computed tomography (CT), magnetic resonance imaging (MRI) and electroencephalogram (EEG) , among others. Of the total number of patients seen, we operate 28 who received omental transplantation in the brain. We chose these 28 patients because CT and / or MRI scans showed morphological integrity of higher brain parenchyma 80%. The rest of the intracranial cavity was represented by atrophy of the cerebral circumvolutions, in fissures, small infarcts in the cerebral parenchyma and discrete ventricular dilatation. In seven patients, CT and / or MRI scans revealed arachnoiditis in chiasmatic cistern, interpeduncular or pontine (Figure 1) and three patients also had arachnoid cyst in the temporal fossa. Were not included in this group, patients with cerebellar atrophy. Fifteen patients were male and 13 female, whose ages ranged from 4.5 years to 24 years. In 22 patients (78.6 %) was less than age 10 years and of these, 15 had moderate malnutrition. Previously, five patients had been operated on hip or feet for tendons rotation.

All patients had motor deficit (hemiparesis, tetraparesis or paraparesis), mental retardation and speech disorders (dysphasia motor, sensory or mixed dysphasia ) to varying degrees, as the cases reported by other authors\(^\text{(7,14,15,28)}\). Twelve patients (42.8 %) suffered from epilepsy (myoclonic, complex partial and / or generalized tonic-clonic seizures ). For example, a 24- year- old man with a history of moderate ICP, he was admitted with tetraparesis, mental retardation, mixed dysphasia and complex partial seizures with secondary tonic-clonic generalization (8 to 12 attacks by day), abnormal EEG in its rate base and frequent paroxysmal EEG discharges .His preoperative CT scans (Figure 2A) showed areas of diffuse microinfarcts in frontal, parietal , temporal lobes ,but predominantly left temporal atrophy. Three of these 12 patients suffered from uncontrollable seizures to the medical treatment and the EEG was
hypsarrhythmic type. As treatment they received diphenylhydantoin (DPH), carbamazepine (CBZ), phenobarbital, valproate and clonazepam, among other drugs. The remaining patients had motor deficits and varying degrees of MBD (also known as attention deficit).

In 24 patients the hemoglobin ranged from 8.5 to 12 g %, hypochromic erythrocytes and protein below normal. Ten patients received full blood transfusion prior to surgery. Previous Informed consent of parents about the surgery, the clinical picture was documented on videotape.

Operation: Under the influence of general anesthesia with endotracheal intubation, the patients were placed in possession supine on the operating table. Subsequently, laparotomy and craniotomy were performed by a team of general surgeons and neurosurgeons, respectively. Basically, the surgical technique was the same as previously reported (16,17,19,21,24).

In abdomen, by means of an incision supraumbilical, we performed a laparotomy. In 15 patients, the omentum was normal (surface normal: 300-1500 square cm)(31) and the remaining tissue was small and thin (related to malnutrition patient) However, in all patients we extirpate 4 cm. of gastroepiploic arcade and the excised surface containing omental vessels.

In skull, by Walker type incision in the temporal region and prior isolation of the superficial temporal artery; we perform a craniotomy with 4 burr holes. The dura centered on the fissure of Sylvius, was opened as a "Y" with the largest segment of the fissure and the other two, addressed to the anterior temporal and frontal lobes. The 3 arachnoid cyst was opened, sucked and removed as much of membranes.

Using the operating microscope, we visualize adhesive arachnoiditis in 18 patients (64.3 %) on the anterior portion of the Sylvian fissure which continued to optochiasmatic region, in varying degrees of severity. We remove segments of these membranes to display terminals and collateral arteries in the region. Through a slot on the anterior third of the fissure, we delve to the M1 segment of the middle cerebral artery, anterior perforated space (APS) and the supraclinoid carotid bifurcation. In the temporal and / or frontal cortex, we observed microinfarcts and atrophy in the circumvolutions of the surgical area. At the level of APS and chiasmatic cistern we found: 1) reduction in the number and size of the anterior perforating arteries, and 2) some collapsed and exsangües perforating arteries and, especially in children with severe adhesive arachnoiditis, Then, after microvascular anastomosis end- to- end by invagination between the superficial temporal artery and the gastroepiploic artery of the omentum; a segment of the graft was placed on the APS and other two, on the temporal fossa and chiasmatic cistern. However, in only 13 patients, the omentum was placed on the APS, because the omental graft was small Twenty patients received transfusion during surgery. Before closing the dura, we placed a Nélaton # 10 probe on the temporal cortex (inner end) with exit behind the scalp incision.

Results: In 21 patients, neurological improvement was observed since the first day of surgery, expressed in their gaze, facial expression and reduction in spasticity in their limbs. The Nélaton probe was removed 24 to 36 hours after the operation, according to coloration subarachnoid fluid drained into the glove and the alertness of the patient. No patient was re-operated. A 8-year-old girl with severe ICP (Figure 1) presented malignant hyperthermia, 8 hours after the operation and the fever lasted 36 hours. Died of systemic complications and was the last patient of this series.

Five days after the operation, neurological improvement was greater in these 21 patients, so much in muscle tone, voluntary movement, gait, speech and behavior.
Seizures disappeared in 12 patients, although they continued with antiepileptic medication during their hospital stay. In the remaining 6 patients, neurological improvement was minimal and was related to the degree of malnutrition. Upon leaving the hospital, the neurological picture was again documented in videotape. A 6-year-old girl with increasing improvement in their motor and language functions until 5 months after the operation, she presented grippe, pneumonia and died in another hospital. Currently, 10 to 26 months after surgery, 26 patients have improved in different degree. In 18 patients, the improvement in gait, posture and mental capacity is evident. Eleven patients walk without family assistance. Similarly, in 15 patients increased the stature body in 2 to 10 centimeters after surgery. Seizures were aborted in 9 patients, but still receiving DPH, valproate or CBZ half dose. The patient of 24 years of age, is without epileptic seizures and received 400 mg of CBZ during the day and 2 mg of clonazapan at nights. A postoperative TC scan (Figure 2B) shows a marked reduction of microinfarcts, and omentum in the temporal fossa. All patients receive clonazepam at night. The 3 patients with uncontrolable seizures to the medical treatment and with hypsarrhythmic EEG; they have experienced a reduction of 80 % to 90 % the frequency and intensity of the seizures. In 10 patients with MBD, the clinical picture (12) has been reversed and in the rest, there is no neurological improvement. The 13 patients who received only, a small segment of omentum on the APS, they have experienced mild improvement, but they continue with recommendations to improve their nutritional status and rehabilitation.

**Figure 1:** MRI scan without contrast of a 8-year-old girl with severe ICP, showing the presence of adhesive arachnoiditis in the chiasmatic, interpeduncular and pontine cistern.
**Figura 2A:** Preoperative CT scan with contrast of a 24-year-old man with moderate ICP, showing diffuse microinfarcts in the frontal and temporal lobes.

**Figura 2B:** Postoperative CT scan with contrast, 12 months after surgery, showing omental tissue in the left temporal lobe, in the patient with moderate ICP.
DISCUSSION

Since April 2002, we know that transplanted omentum on the carotid bifurcation, APS, and left temporal lobe in a 10-year-old girl with severe ICP, we can improve all the neurological picture\(^{(21)}\). She was the first patient who received omentum for this disease. Today, 13 years after the operation. The patient is independent and she has a similar behavioral to her age (22 years), except by a discrete motor dysphasia. The epileptic seizures have been aborted, but present theta waves and occasionally delta wave during sleep, the patient continues with 1 mg of clonazepam at night.

Between October 1987 and 2004, we known that the omental transplantation to different regions of the nervous system; this tissue causes formation of blood vessels and through them, the underlying and adjacent nerve tissue to the omentum, it receives an increase in blood flow (revascularization), oxygen, neurotransmitters, neurotrophic factors and adipocytokines\(^{(9,17,22,24,31)}\). But about 2004 and then in 2006, two important events for brain reconstruction was discovered\(^{(15,21)}\). Firstly, the omentum is potential origin of mesenchymal stem cells\(^{(4)}\) and second, the subventricular zone of the lateral ventricles of adult human brain, is also a source of neural stem cells\(^{(11)}\). Therefore, we believe that neurological improvement of our first patient operated by ICP\(^{(21)}\), was due to: First, revascularization of the underlying brain parenchyma (APS, hypothalamus, anteromedial temporal cortex, posterior frontal cortex, optic chiasm and orbitofrontal cortex) and adjacent (territory of the circle of willis and perforating arteries) to the omentum. Second, cell proliferation (neurogenesis and gliogenesis) from two sources: 1) mesenchymal stem cells from the omentum, and 2) neural stem cells from the subventricular zone, especially from the dentate gyrus of the hippocampus. Currently there are more information about the presence of stem cells in the omentum\(^{(25,26)}\) and in the subventricular zone of the adult brain\(^{(1,5,6,10)}\).

So, based on the above mentioned observations, we believe that neurological improvement in our patients reported here are due to: 1) the degree of morphological integrity of the brain parenchyma (greater than 80%); 2) to the surface and thickness of the transplanted omentum, 3) the reduction or elimination of seizures by revascularization in the epileptogenic foci\(^{(18-21,24)}\); 4) the degree of patient nutrition and 5) the time postoperative evolution. Therefore, unlike intravenous\(^{(8,27)}\) or subarachnoid infusion\(^{(3,27)}\) of mesenchymal stem cells performed by other authors; we think that our surgical method have more advantages, because revascularize to the injured brain parenchyma and provides mesenchymal stem cells from the omentum\(^{(4,25)}\) and moreover, promotes the proliferation, migration and differentiation (neurons and glia) from the neural stem cells, located in the subventricular zone of the lateral ventricles\(^{(1,5)}\).

Finally, we comment that the use of postoperative anti-epileptic medication, was in order to prevent discharges from epileptogenic zones\(^{(19)}\), located in the neocortex or within the medial temporal cortex of the cerebral hemisphere contralateral to surgery. The CBZ as the DPH not have stock in the limbic system, but clonazepam\(^{(13,15)}\). We use clonazepam in all patients and especially at night; because the neuronal activity in the hippocampus is more active during NREM sleep\(^{(13)}\). The clonazepam increases the inhibitory postsynaptic potential in allocortex (archicortex + paleocortex), whereas the DPH and CBZ act in the neocortex and its actions are independent of the hippocampal formation and amygdala\(^{(13)}\). The valproate, especially magnesium valproate has some action in
the medial temporal lobe to be related to GABA receptors in the hippocampus\(^{(13)}\). In relation to the increased stature body in 15 patients, we believe that was due to two factors: 1) revascularization of the arcuate nucleus of the hypothalamus, main producing hypothalamic nucleus of growth hormone-releasing hormone\(^{(23)}\) and 2) improvement of the nutritional status.

**CONCLUSION**

To date, it is possible to reconstruct the brain of patients with ICP and thus, to improve this public health problem. Based on our results, we believe that neurological improvement was associated with: 1) the morphological integrity of the brain (greater than 80%), 2) amount of transplanted omentum; 3) surgical findings in the chiasmatic cistern, 4) degree of vascular abnormalities in the surgical area; 5) direct implantation of stem cells from the omentum, 6) to favor the development of neural stem cells, and 7) the rehabilitation. For these reasons, we think that our surgical technique have more advantages than a simple subarachnoid or intravenous injection of stem cells. Because these therapeutic modalities not improvement the arachnoiditis in the chiasmatic cistern nor revascularize to the damaged brain parenchyma.

**REFERENCES**


