OTI (HBOT) Efficiency in Decompensated-Complicated Parkinson’s Disease

Excerpt from the 12th International Congress on Hyperbaric Medicine

A. Borromeo, U. d'Orsi, G. Leandro, S. Maitan, P. Longobardi
1 Istituto di Clinica Neurologica - Bologna University,
2 Istituto di Ricovery c Cura a Carattere Selentifico (IRCCS)
"G. De BEEIW' - Castellana Grotte (Bari),
3 SeMzio di Anestesia c Rianimazione Usl 37,
4 Centro Iperbarico - Ravenna

INTRODUCTION

Today the routine anti-Parkinson therapy is sufficiently standardized. The biggest problems arise with decompensated or complicated Parkinson's Disease.

For "decompensated" Parkinson's Disease is meant that illness which produces undesired reactions to the therapy, or which does not respond to treatment. "Non-responder" patients to laevo-dopa belong to this category, as do those with long distance L-Dopa syndrome (LTLS) and those with various reactions brought on by the cure (dyskinesia, on-off, freezing, etc.), as well as patients with young or very old forms, which normally have more noticeable side effects, not only from L-Dopa but also from other anti-Parkinson medicines.

For "complicated" Parkinson's Disease is meant the illness with gravely disabling secondary or satellite phenomena, such as psycho-organic (or demential, already called "Parkinson-plus") decline, the presence of pathologies concerning moods (especially depressive), pathological types of induced personality (e.g. with grave "emotional inflexibility" and/or notable obsessive-phobia tracts, excessive introspection, etc.). In other words, the presence of grave autonomic disturbances.

The two forms of the disease (decompensated-complicated) have very similar treatments, but in some cases they are also selective.

In neurological pathologies it has been demonstrated that the oxygen administered in a hyperbaric environment up to the maximum partial
pressure of 1.6 ATA determines a balancing of the glucidic cerebral metabolism, with a return to normal values in patients with cerebrovascular pathologies: instead, at a pressure of 2 or more ATA the glucidic neuronal metabolism is compromised, with the amount varying from one encephalic region to another, and it is dose-dependent. The clinical reactions of hyperoxy neurological toxicity in rats were always preceded by an increase in the cerebral use of glucose.

The hyperbaric oxygen in cerebral pathologies is therefore not dangerous and has a beneficial effect at partial pressure of 1.6 ATA with maximum tolerability up to 2 ATA.

RATIONAL

Among the pathogenetic hypotheses of Parkinson's Disease it was seen that various toxic matters (pesticides or herbicides such as paraquat, disquat, parathon, ditiocarbamatii, etc.) can induce parkinson pathologies. However, the most specific example concerns methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) by means of the product (MPP) of its oxidation, catalysed by MAO-B. Furthermore, there is a secondary reduction of the "I" complex of the mitochondrial chain (demonstrated in the substantia nigra, as well as in the muscles and blood platelets) and a reduced transfer of electrons for the formation of ATP (fundamental for cellular metabolism), therefore a reduction in the formation of glutatan appears, with a parallel increase in the free radicals (FR) for its peroxidation.

The excito-toxic mechanism leads to a flow of cations mediated by amino acid receptors which cause neurotoxic effects on the part of the glutamate and the erogenous excito-toxins.

Excessive activation of Ca-dependent enzymes involved in the neuronal functions (e.g., nitro-oxidesyntethasis, C. proteinchinas, phospholipasis and proteasis) is noted in the alterations in the homeostasis of intercellular calcium. This leads to damage to the cellular membranes as well as a changed energetic support (due to inhibition of the respiratory chain enzymes).

D.F. Wilson (1979,2) and A.C. Bylund-Fellenius have shown that by administering normobaric oxygen to cellular cultures or even to a group of patients with claudication of various aetiologies, who later underwent a muscular biopsy, an increase is obtained in the glycolysis enzymes and in the citric acid cycle (Krebs). An increase in energy is particularly noticed (ATP/ADP; of inorganic phosphate) and also in the oxide-reductive potential (understood as the redox of the NAD cito-plasmatic couple) of the muscle tissue. A.G. Nelson et al (1993,4) showed that the O.T.I. determines an increase in the activity of some enzymes in the Krebs cycle which is statistically greater than the one obtained with the administration of pure normobaric oxygen (56% for the citrate-syntethasis and 24% for the alpha-glycerophosphate dehydrogenesis). The authors consider that the repeated enzyme inactivation due to repeated exposure to OTI represents a stimulation which deter- mines an increase in the cellular enzymatic activity. In synthesis, this stimulation is secondary to the alternating of hyperoxia and hypoxia.

The main reason for our study is that by administering hyperbaric oxygen
to patients with decompensated and complicated Parkinson's Disease, it is possible to increase the mitochondrial production of ATP and phosphocreatin, determining an increase in neuronal energy, in such a way as to compensate the illness or resolve its complications.

The second reason relative to the OTI action mechanism in Parkinson's Disease is based on the fact that in patients with this pathology greater activity is noted in the mitochondrial fraction of the superoxidedismutasis, in some regions cerebral, among which, mainly the black substance.

Cohen et al (1976,5) considered damage by the free radicals to the nigrostriatal catecolaminergic neurons in Parkinson's Disease. Spatz (1922,6) discovered quite a large amount of iron in the pale globe and in the black substance in the brains of both men and monkeys. The iron ionia can act as catalysts of the lipidic peroxidation, reacting directly with the lipids of the membrane and the oxygen. Therefore, in these areas and to a lesser degree also in the spinal marrow, in the superior olivary complex, in the ventral cochlear nuclei and in the nuclei of the spinal part of the fifth cranial nerve where there is a greater concentration of iron ionia (at least in rats), there is special vulnerability to the reactions of the oxygen free radicals.

Borromei and colleagues carried out a bibliographic revision of the previous studies associating clinical control with the anatomical-pathological comparison in patients with Parkinson's Disease, which confirms what has already been mentioned. In cerebral autoptic examples, significant reductions in the scavenger levels have been demonstrated (GSH, cathalasis, SOD Cu and Zn dependent) and in malonil-dialdeide exclusively in the substantia nigra of this kind of illness.

The destruction of the neurons in Parkinson patients could therefore also be caused by FR derived from quinones of the dopaminergic neurons, rich in catecolamines and peroxides generated by the MAO. Cohen speculated that the citotoxic FR, produced by the oxidating activity of the monamines, can be involved in the destruction of the dopaminergic neurons in Parkinson's Disease.

In primates the nigro-striatal dopaminergic neurons contain a high concentration of neuromelanine pigment. It has been considered that Parkinson's Disease may derive from the citotoxicity of the products due to the metabolism of the catecolamines and the oxidation of the melanine. Therefore, the premature cellular destruction of the dopaminergic neurons would come about in various ways, but always connected with the free radicals. Perry and colleagues (1982,11) observed that the levels of GSH are significantly fewer in the black substance, whose neurons are more vulnerable compared to other regions of the human brain and that in the brain of Parkinson patients this amount is almost zero. Since reduced glutation is an important endogenous antioxidant, as a co-factor for the scavenger enzyme activity against the free radicals of the glutation-peroxidasis, it is probable that the substantia nigra is the encephalic region which is more sensitive to the toxic effects of the radicals.

These observations and research pose the problem of whether to treat
patients with initial signs of Parkinson's Disease with inhibitors of the B monoamino oxidase and/or with other free radical scavengers, such as vitamin E, GSH and ascorbic acid, in order to stop the progressive destruction of the nigral cells.

The idea is made more suggestive by bromocriptine's evident antioxidising effect. This medicine is often used in the treatment of Parkinson's Disease, especially at the beginning. The same is true of selegiline, a selective MAO B inhibitor (Tetrud and Langston 1990), which undoubtedly has a scavenger function and possibly can even be used as preventive therapy in the illness, as well as pergolide which could have neuroprotective effects. The DATATOP ("Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism") group speaks precisely of "protective" therapy.

Correctly administered, the hyperbaric oxygen therapy favours the production of defensive scavenger enzymes, especially superoxido dismutasis (SOD) and cathalasis. Kapp (1993) injected rats intravenously with liposomes containing SOD and cathalasis. At a cerebral level the activity of these enzymes increases respectively by 2.7 and 1.9 times after 15 minutes from the liposome injection. Furthermore, these rats, which had this treatment 2 hours before a hyperbaric treatment at 6 absolute atmospheres with 100% oxygen respiration (an experimental condition meant to cause convulsions in the rats), show an increase in the latency period before the convulsions begin, of three times more than the controls. This protective effect is dose dependent and is mainly due to the increase in the cathalasis activity. Many experiments have confirmed that during exposure to hyperbaric oxygen with quite long periods between treatments, a significant increase in the scavenger substances can be noted, especially in SOD and cathalasis. This may explain the clinical benefits which can be obtained with this therapy, administered at the right moment, in neurological pathologies such as Parkinson's Disease.

MATERIALS AND METHODS

A) Case histories

15 patients suffering from Parkinson's Disease were treated (8 men and 7 women), with an average age of 65.5 years (age limits 46 - 85).

The illness can last from a minimum of 6 to a maximum of more than 25 years.

The etiopathogenesis noted are: 7 idiopathic (46.7%); 4 vasculopathic (26.7%); 3 post-encephalic (20%, one case of Spanish influenza, 2 of Asiatic), 1 other kind (6.6%)

Clinical type: 8 mixed forms (53.3); 4 hypercinetic (26.7%); 3 acinetohypertonic (20%). Pathological topography: 10 bilateral (66.7%); 3 sin. unilateral (20%), 2 dx unilateral (1 3.3%) Type: 10 decompensated (66.7%), 5 complicated (33.3%) of whom 4 vasculoparic and 1 another type.

B) OTI (HBOT) chart proposed
1) for patients with decompensated or complicated Parkinson's Disease (for causes other than vascular):

a) 15 hyperbaric oxygen therapy treatments at 1.9 ATA (absolute atmospheres) for 80 minutes per treatment (respiration cycles alternating between 10 minutes in pure oxygen and 2 minutes in air).

b) maintenance therapy: 5 treatments (1.9 ATA for 80 minutes) every 3 months.

We adopted respiration cycles of 10 minutes respiration in oxygen, each period alternated with pauses of respiration in air for 2 minutes, because by monitoring the patients with a transcutaneous oximetre it was seen that with this method we can reach excellent values of tissue oxygenation without starting up vasospasm phenomena and avoiding excessive falls in the transcutaneous oxygen tension during the pause in air (so that a constant oxygen concentration can he kept at tissue level).

2) for patients with complicated Parkinson's Disease due to vascular causes:

a) 25 daily OTI (HBOT) treatments at 2.5 ATA for 90 minutes (cycles of 10 min. of 02 + 2 min. of air). b) maintenance therapy: 5 treatments (2.5 ATA x 90 min. 02) every 3 months.

The difference between the two protocols is due to the results obtained during an early experience where it was shown that patients suffering from complicated Parkinson's Disease due to vascular causes did not respond well to the therapeutic chart proposed for the other kinds of Parkinsonism.

C) Therapeutic strategies The patients of neurological interest need to be treated at a maximum pressure of less than 2.0 absolute atmospheres (preferably 1.9 ATA) so that the cerebral vasoregulator phenomena are not influenced by the relative hyperoxia. Furthermore, within this bathymetry the production of nitric oxide (NO) is stimulated which, within certain limits, has an important role in vasoregulation, as well as a reduced production of oxygen free radicals balanced by a notable stimulation of the scavengers. With a larger bathymetry, not only does the OTI (HBOT) not produce favourable effects, it can actually determine a deterioration.

It is also useful to control the transcutaneous oxygen pressure at a systematic level (with a Clarke electrode placed in the space above the left clavicle) at least before beginning the OTI (HBOT), at the 1st and at the 10th hyperbaric treatment.

In patients with Parkinson's Disease not on a vasculopathic base (11, equal to 73.3% of our series) the values were normal. In patients with vasculopathic Parkinson's Disease (4 equal to 26.7% of our series) the transcutaneous oxygen pressure was initially less than normal (60-80 mmHg during the evaluation in environmental air and between 200 and 500 mmHg during the first treatment with hyperbaric oxygen). It was however shown to be normal at the second reading taken during the 10th
treatment.

Only one patient suspended the hyperbaric treatment because of a middle
catarrhal otitis which made compensation of the middle ear difficult. None
of the patients abandoned the treatment because of psychopathological
claustrophobia, sometimes mentioned in literature as a cause of drop-out.

RESULTS

The patients were clinically evaluated with both the Webster rating scale
(WRS) and the Crichton Geriatric Behavioural Scale (CGBS). The
neurological exam was done before beginning, half-way through and at
the end of the first hyperbaric therapy cycle, and at the beginning and
end of each maintenance cycle. The Spearman Rank correlation
coefficient was used as a test for the statistical analysis, as this appeared
to be the most suitable for the statistical evaluation of our kind of data.

The two scales used do not show significant correlation ($r = 0.08$) but the
variation after the therapy shows significant correlation ($r 0.7$) between
the two scales.

This means that the two scales "see" different things but the patients who
show an improvement in one scale also show it in the other.

CONCLUSIONS

The first comprehensive evaluations of the results, based on an objective
clinical control but bearing in mind the CGBRS index and the Webster
scale, seem to be favourable and encouraging.

### Webster rating scale (WRS)

<table>
<thead>
<tr>
<th>Pre - OTI (HBOT)</th>
<th>values between 18 and 32 (average 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>post - OTI (HBOT) index</td>
<td>values between 13 and 23 (average 18)</td>
</tr>
<tr>
<td>index</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

### Crichton Geriatric Behavioural Rating Scale (CGBRS)

<table>
<thead>
<tr>
<th>Pre - OTI (HBOT)</th>
<th>values between 17 and 39 (average 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>post - OTI (HBOT) 21.5) index</td>
<td>values between 12 and 31 (average</td>
</tr>
<tr>
<td>index</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

### Webster Rating Scale - WRS

<table>
<thead>
<tr>
<th>Bradykinesia of the hands, including writing</th>
<th>2.5</th>
<th>1.6</th>
<th>0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>2.7</td>
<td>1.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Posture</td>
<td>2.1</td>
<td>1.5</td>
<td>0.06 (n)</td>
</tr>
<tr>
<td>Oscillation of the limbs</td>
<td>2.1</td>
<td>1.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gait</td>
<td>3.2</td>
<td>1.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Tremors</td>
<td>2.3</td>
<td>2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Facial expression</td>
<td>2.2</td>
<td>1.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Seborrhoea</td>
<td>2.2</td>
<td>1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>Diction</td>
<td>2.3</td>
<td>1.3</td>
<td>0.0005</td>
</tr>
<tr>
<td>Autonomy</td>
<td>2.7</td>
<td>2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Note: n.s. = not significant*

### Crichton Geriatric Behavioural Rating Scale - CGBRS

<table>
<thead>
<tr>
<th>Item</th>
<th>Pre - OTI (HBOT)</th>
<th>Post - OTI (HBOT)</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in dressing</td>
<td>3.3</td>
<td>2.1</td>
<td>0.00002</td>
</tr>
<tr>
<td>Nourishment</td>
<td>2.1</td>
<td>1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Continence</td>
<td>2.7</td>
<td>2.2</td>
<td>0.06 (n.s.)</td>
</tr>
<tr>
<td>Sleep</td>
<td>2.4</td>
<td>1.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Objective mood</td>
<td>2.5</td>
<td>2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Subjective mood</td>
<td>2.2</td>
<td>1.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Mobility</td>
<td>2.8</td>
<td>2.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Orientation</td>
<td>1.9</td>
<td>1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Communicativeness</td>
<td>2.5</td>
<td>1.8</td>
<td>0.006</td>
</tr>
</tbody>
</table>

By "favourable" results we do not mean an inversion in the tendency of the illness substantial modifications in the severity index. We refer to the improvement in psychomotorial capacities, connected with the mood, identifiable in some precisions of the two, universally accepted scales.

Webster has pointed out significant recoveries of the upper bradykinesia (with improvement in writing, p < 0.001), of gait (p < 0.002), of facial expression (p < 0.001) and of speech fluency (p < 0.0002). Crichton noted that the difficulties dressing were favourably modified (p < 0.0002), with significant variations in tone of the subjective mood (p < 0.01) and a parallel improvement in total QOL compared to before the treatment. In other words, with OTI (HBOT) not only there an improvement in the classical symptoms of Parkinson's Disease (mimic expression, speech, writing ability, movement), but also in the autonomic diso and in the state of depression, as happens also in polyneuropathic patients. In this study there are no significant results, especially concerning posture, tremor, orientation and sphincter- al continence.

It proved to be necessary to differentiate the hyperbaric treatment in vasculo-complicated parkinsonism with respect to patients who were carriers of Parkinson Disease (decompensated and/or complicated) of the idiopathic or post-encephalitic kind.

We would point out that our data will be verified after a further, prolonged follow-up. In our series the controls vary from 6 to 18 months with an average of 9 months which does not yet allow us to state that the modifications which we observed are permanent.

It is possible that complementary therapy with OTI (HBOT) can be used not or
along with the standard, anti-Parkinson medicines (which they do not substitute) but also with substances which have recently come into use, such as Gdnf (glial cells neurotrophic factor) recently proposed by Olson (1995), whose therapeutic effects appear at least theoretically to benefit from the collateral use of hyperbaric oxygen.

Recent studies have progressively clarified the use of neurotrophic factors which could influence the development and the survival of the nervous cells. Experiments are being carried out, such as Olson's, based on the assumption that the neurotrophic factors are not only able to impede inhibition of the protein synthesis but also to stimulate the synthesis with a parallel increase in the release of neurotransmitters and the recovery of the compromised synapsis.

Another possible use of OTI (HBOT) in Parkinson's Disease concerns the start of the oligo or monosymptomatic phase of the illness. In other words, to use a wider but not proper term for preventive treatment.

For example, using as a clinical marker the internal tremor which can precede by months or years the beginning of the illness, it is to be verified if hyperbaric oxygen therapy can delay the start of extrapyramidal symptoms.

REFERENCES

5. Cohen G. - Catalase, glutathione, peroxidase, superoxidase dismutase and cytochrome p-450. In: Lajtha A (ed) "Handbook of Neurochien-
11. Perry T.L. and coil. - Parkinson's disease: a disorder due to nigral gin-