Brain Ischemia and Hypometabolism Treated by Ozone Therapy

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Summary
Background: Radiation-induced brain injury (RBI) and low-perfusion brain syndromes are mediated by ischemia and hypometabolism and have limited treatment options. Ozone therapy as treatment in vascular diseases has been described, but the effects on brain tissue have not been well documented. Case Report: We describe a 75-year-old patient with vascular risk factors and meningioma who was treated with stereotactic radiosurgery. 14 months later the patient presented with progressive clinical impairment despite the use of acetylsalicylic acid and corticosteroids. Clinical and imaging evaluations before/after ozone therapy were done by magnetic resonance imaging (MRI), computed tomography (CT), single photon emission computed tomography (SPECT), and positron emission tomography (PET); performance status assessment was done using Barthel Index and World Health Organization/Eastern Cooperative Oncology Group Scale (WHO/ECOG Scale). Ozone therapy was performed by autohemotransfusion. Results: Basal images showed brain areas with ischemia and hypometabolism compatible with ischemic processes and/or RBI. There were no changes in MRI or CT scan images following ozone therapy. However, improvements in brain perfusion and metabolism were demonstrable with SPECT and PET; they correlated with clinical development and performance status scales. Conclusion: This report supports our previous works about the effect of ozone therapy in cerebral blood flow, and it suggests the use of ozone therapy in ischemic and hypometabolic brain syndromes such as stroke or RBI.
Introduction

Cerebrovascular diseases and radiation-induced brain injury (RBI) are mediated by ischemia and hypometabolism. Ischemic brain syndromes have significant clinical and social repercussions. In the USA, approximately 610,000 people each year had de novo stroke and about 185,000 recurrence of the disease. Mortality data from 2006 indicate that stroke accounted for approximately 1 in every 18 deaths (around 130,000 people). The estimated direct and indirect costs for the year 2010 are USD 73.7 billion [1]. Stroke and RBI not only share similar features, but also have limited therapeutic options.

Ozone therapy has been used for the last 100 years in the treatment of ischemic disorders, particularly those of the lower limbs, although there are no data from clinical trials yet. It has been described that ozone can enhance antioxidant systems and regulate immune/inflammatory response [2–4], improve vascular rheology [5–7], and increase blood flow in carotid and middle cerebral arteries [8] and tissue oxygenation in hypoxic tissues [9]. We have previously treated several ischemic syndromes [10] and radiation-induced side effects [11, 12] with this procedure. However, the effects of ozone therapy on brain tissues have not been well documented.

Case Report

A 75-year-old woman receiving treatment for high blood pressure and diabetes was diagnosed and treated for epilepsy. She received valproic acid after an intolerance to phenytoin had been observed. Magnetic resonance imaging (MRI) showed meningioma in the anterior right temporal lobe and vasogenic edema in the ‘temporal and parietal’ right lobes. She underwent stereotactic radiosurgery. A gamma-knife device was used to administer a single fraction of radiotherapy. Eight months later she presented with Parkinson’s syndrome, and treatment with levodopa was initiated. However, general impairment and bradypsychia were progressive, and 14 months after the radiosurgery she presented hyponatremia (Na+ of 120 meq/l) and low osmolality (248 mosm/l). The diagnosis of inappropriate antidiuretic hormone secretion (SIADH) syndrome was made.

MRI showed no changes in the anterior right temporal lobe, but there was a signal increase in 2 previously altered sites: juxta-cortical ‘temporal and parietal’ right and periventricular lobes; both compatible with white matter alterations secondary to radiotherapy (fig. 1, upper panel). In these basal pictures, areas of leukoencephalopathy in MRI correlated with areas of hypoperfusion (fig. 1, middle panel) and hypometabolism (fig. 1, lower panel). Single photon emission computed tomography (SPECT) with technetium-99m ethylenediamine dimer (ECD-SPECT) showed a decreased blood perfusion in the ‘temporal and parietal’ right lobes which suggested vascular etiology such as an ischemic process and/or RBI (fig. 1, middle panel). Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) showed 1) a slight increase in metabolism, as measured by the maximum standardized uptake value (SUVmax) of 1.8 in the anterior right temporal lobe (meningioma) compared to the SUVmax of 1.5 in the contralateral area of the anterior left temporal lobe and 2) a decreased metabolism in ‘temporal and parietal’ right lobes with SUVmax value of 1.3; features compatible with edema, ischemic process and/or RBI (fig. 1, lower panel).

The patient showed progressive clinical impairment necessitating several hospital admissions despite the use of acetylsalicylic acid and corti-
Ozone Therapy in Brain Ischemia and Hypometabolism

Table 1. Clinical development of some nervous system disorders before and after ozone therapy

<table>
<thead>
<tr>
<th>CTC/CTC a</th>
<th>Before ozone therapy</th>
<th>After ozone therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia b</td>
<td>grade 3</td>
<td>grade 0</td>
</tr>
<tr>
<td>&lt;130-120 mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>grade 2</td>
<td>grade 0</td>
</tr>
<tr>
<td>moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory impairment</td>
<td>grade 2</td>
<td>grade 0</td>
</tr>
<tr>
<td>moderate memory impairment; limiting instrumental ADL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>grade 2</td>
<td>grade 0</td>
</tr>
<tr>
<td>moderate symptoms; limiting instrumental ADL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>grade 2</td>
<td>grade 1</td>
</tr>
<tr>
<td>moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum ± moderate increase in SAS and/or moderate ventriculomegaly</td>
<td>asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or &lt;1/3 of susceptible areas of cerebrum ± mild increase in subarachnoid space and/or mild ventriculomegaly</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular ischemia</td>
<td>grade 2</td>
<td>grade 1</td>
</tr>
<tr>
<td>moderate symptoms</td>
<td>asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td></td>
</tr>
</tbody>
</table>


b There were 4 different episodes of hyponatremia: 2 grade 2 and 2 grade 3.

ADL = Activities of daily living, T2/FLAIR = T2-weighted fluid attenuated inversion recovery.

costeroids and appropriate control of high blood pressure and hyperglycemia. The potential diagnoses were 1) ischemic process and/or 2) RBI. No additional standard management was planned, but the patient’s family requested further treatment. We offered her some therapeutic options which we used in our university hospital for selected patients with ischemic syndromes. Ozone therapy was her preference. Informed consent was obtained before the commencement of treatment. Over a period of 11 months 58 sessions of ozone therapy were administered, using a one-way central venous catheter (Hickman®) as follows: 150 cc/m² (blood/body surface); O₃/O₂ concentration 30 μg/ml initially and slowly increasing to 60 μg/ml. The sessions had a low frequency and progressively dropped off from 3 sessions per week in the first month to once per month for the last months.

During and after ozone therapy a clear clinical improvement was assessed by 2 functional scales. Performance status before/after treatment was 65/100 (from 0 to 100, where 100 is better) as measured by Barthel Index [13] and 3/1 (from 0 to 4, where 0 is better) as measured by World Health Organisation/Eastern Cooperative Oncology Group Scale (WHO/ECOG Scale). Table 1 describes additional clinical information before and after ozone therapy in relation to some nervous system disorders using the Common Toxicity Criteria of the National Cancer Institute. Clinical improvement was maintained up to the last follow-up which was 30 months after terminating the ozone therapy. There were no new episodes of hyponatremia. MRI and computed tomography (CT) did not show any changes at 4, 19, or 30 months. However, increases in brain perfusion and metabolism relative to basal values were noted. ECD-SPECT at 3 months of treatment showed an overall increase in blood perfusion in lesions of the ‘temporal and parietal’ right lobes, as well as right basal ganglia (fig. 2, upper panel). FDG-PET at 5 months of ozone therapy showed an overall increase in metabolism (approximately 25%), including hypometabolic lesions in ‘temporal and parietal’ right lobes as well as right basal ganglia (fig. 2, lower panel). The clinical improvement paralleled the increased perfusion observed by ECD-SPECT at the 3rd month of treatment, which was maintained at the last follow-up at 30 months after terminating ozone therapy, that is 40 months after the initiation of ozone therapy.

Discussion

This case suggests that ozone therapy could improve blood flow and metabolism in ischemia-related syndromes such as RBI or stroke. Clinical improvement (general physical status) was long-lasting sustained. For this patient the potential diagnoses were: 1) ischemic process with risk factors, albeit not of a typical clinical presentation, and 2) RBI, albeit ‘temporal and parietal’ vasogenic lesions visible in MRI were present prior to radiosurgery; periventricular vasogenic lesions were distant from the highly limited irradiated volume of radiosurgery. Probably both factors were implicated in the ischemic and metabolic alterations in this patient. The existing high blood pressure and diabetes were risk factors for vascular diseases and also for RBI, while brain irradiation increases the risk of cerebrovascular diseases and stroke [14].

Stroke, the main presentation of cerebrovascular diseases, has limited therapeutic options. For aspirin consistent benefi-
cial effects have been shown but it is of only limited value in preventing new attacks [15], while antithrombotic treatment with recombinant tissue plasminogen activator has been somewhat effective if applied within the first 3 h of the epi-

sode, but only in selected patients [16].

RBI is also mediated by vascular, inflammatory and degener-

ative changes, including demyelization and leukoencepha-

lopathy [14]. Limited approaches are available for RBI when symp-

toms are progressive and lesions are not suitable for surgery. Proposed therapies with the objective of improving blood perfusion/oxygenation include anticoagulants [17], hyperbaric chambers [18, 19], spinal cord stimulation [20], and modification of the radiation-induced pro-oxidative status using vitamin E [21].

In ischemic processes and in RBI decreased blood flow leads to decreased oxygen delivery and ischemia/reperfusion. These induce a cascade of metabolic disorders such as decrease in aerobic glucose metabolism (and reduction of ATP levels) and inflammation changes followed by tissue acidosis and increase in free radicals. Additionally, ischemia leads to excitotoxicity mediated by glutamate receptor activation and increase in free radicals. These induce a cascade of metabolic disorders such as decrease in aerobic glucose metabolism (and reduction of ATP levels) and inflammation changes followed by tissue acidosis and increase in free radicals. Additionally, ischemia leads to excitotoxicity mediated by glutamate receptor activation and the subsequent increase of nitric oxide and calcium accumulation, resulting in a damage of the pump systems and serious disturbances in ionic conductance which are associated with apoptosis and necrosis of neurons [22] and white matter injury [23]. Ozone therapy could regulate these mediators and reduce the pathological oxidative stress, as demonstrated in liver [3] and renal [4] rat models.

Within this context, other interesting actions of ozone ther-

apy have been described: improvement in vascular rheology [5, 6], increase in blood flow in the carotid and middle cerebra-

ral arteries [7], improvement in tissue oxygenation in hy-

doic tissues [8, 9], enhancement of antioxidant systems, and modulation of immune/inflammatory response [2–4]. More

information on vascular and metabolic effects in brain tissues can be found in a recent review [24].

Our findings are further supported by isolated preclinical [25] and a clinical study [26] in ischemic brain syndromes as well as in radiation-induced tissue toxicity reports [11, 12].

Finally, of note is that clinical development correlated better with functional imaging techniques than with MRI or CT scan. Functional imaging techniques could be more useful in assessing the effects of ozone therapy in these syndromes, and they should be more extensively evaluated in clinical studies.

This report supports our previous works about the effect of ozone therapy in cerebral blood flow, and it suggests the potential usefulness of ozone therapy in the treatment of ischemic/metabolic brain syndromes such as those secondary to cerebrovascular diseases and/or RBI. Further research is planned.

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ing of the European Cooperation of Medical Ozone Societies (Baden Baden, Germany, November 2008), the II. Meeting of the World Federation Oxygen-Ozone Therapy (Madrid, Spain, December 2008), the National and International Ozone Therapy Congress (Istanbul, Turkey, December 2009) and the International Meeting of Ozone Therapy Schools at the Royal Academy of Medicine (Madrid, Spain, June 2010).

Disclosure Statement

The authors have no conflict of interest.

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