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ECT as Used in Psychiatry Temporarily Opens the Blood-Brain Barrier: Could This be Used to Better Deliver Chemotherapy for Glioblastoma

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Glioblastoma remains a poor-prognosis cancer. We review research showing evanescent opening of the blood-brain barrier, BBB, after electroconvulsive treatment, ECT. ECT as currently used in psychiatry for treatment-resistant depression has been in continuous use throughout the world since introduction in the late 1930's. Post-ictal BBB opening phenomenon might be safe enough to use to deliver chemotherapeutic agents that would not otherwise cross the BBB. Although the main mass of tumor in glioblastoma has a relatively leaky BBB, the invasive paucicellular migratory microsatellite glioblastoma cells that become the origin of recurrent tumor are supplied by normal poorly-permeable capillaries, preventing ready access of potentially useful chemotherapy drugs like doxorubicin or methotrexate. These microsatellites go on to kill.

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Modern ECT uses deep neuromuscular blockade and cardiovascular stabilizing drugs such that muscular contractions and increases in intracranial pressure are minimized, yet the electroencephalogram shows a typical grand mal seizure. Post-ECT BBB opening allows transgression of > 4 kDa peptides, potentially comfortable enough to give free access to brain tissue of doxorubicin or methotrexate for example. Even drugs that are said to cross the BBB, such as temozolomide, the current mainstay chemotherapy drug in glioblastoma, do so only at ~20% of plasma levels. Many potentially useful drugs achieve brain tissue levels <1% of blood levels. We conclude that if careful step-wise study can establish safety, by delivering chemotherapy immediately after ECT we may open new and more effective treatment avenues for glioblastoma.

Keywords: Blood-brain barrier; chemotherapy; electroconvulsive treatment; glioblastoma.

1. INTRODUCTION

To dare is to momentarily lose footing- by not daring we lose ourselves. [At vove er at miste fodfæstet et kort øjeblik - ikke at vove er at miste sig selv.] Søren Kierkegaard, 1813-1855.

Glioblastoma is a difficult-to-treat cancer, prognosis having improved little in the last decades [1]. In this short paper we review data showing that electroconvulsive therapy, ECT, as used to treat severe depression, opens the blood-brain barrier, BBB that could result in better access of cancer chemotherapeutic drugs to glioblastoma. Although controversial among a minority, ECT is currently [anno 2012] accepted by most in the medical community and used as an orthodox third-line treatment of resistant depression around the world [2-6]. Not controversial is that glioblastoma is a deadly cancer, the prognosis for which hasn't improved a lot in the last decade despite much effort at finding new treatments, often at the cost of high morbidity and some mortality from treatment itself [7,8]. Comments from 1998 on glioblastoma such as "Disease relapse after both radiotherapy and chemotherapy is invariably due to recurrence within 2 cm of the original lesion" [9] when median overall survival was 9 months, remain largely true today in the temozolomide era when median overall survival is 15 months [10].

One reason for glioblastoma's treatment resistance is the special capillaries comprising the BBB [11-13]. Brain capillaries have tighter junctions between endothelial cells allowing less free passage [both ways] of solutes, including chemotherapy agents, than do capillaries in other organs. For example, the main chemotherapeutic drug for glioblastoma currently is temozolomide. This achieves brain tissue levels about a fifth of that obtained in blood or other organs [11,14,15]. Secondary drugs like irinotecan achieve even less [16].

Although BBB within the main glioblastoma mass are inherently quite leaky, areas of surrounding, otherwise normal brain that bear centrifugally migrating single glioblastoma cells have intact BBB. Even after apparent total resection these microsatellites invariably go on to kill patients, so it is the intact BBB of otherwise normal brain within several cm. of the resection cavity that are the target of BBB opening efforts in glioblastoma treatments.

There is however a caveat. We review data below behind previous recommendations not to use ECT in the presence of intracrainial tumors. We review past research data indicating ECT as used by psychiatry for the last six decades, but using modern neuromuscular blockade and cardiovascular stabilization, and maneuvers to keep intracrainial pressure from

rising, might indeed allow ECT be of low enough risk that the benefits outweigh these risks in this otherwise uniformly fatal disease.
As in the Kierkegaard quote above, we are not advocating heedless daring but rather a thoughtful, careful evaluation of an idea that may initially generate a loss of footing. Delivering ECT to patients with glioblastoma just prior to chemotherapy is admittedly at first glance disconcerting. However, with step-wise study to determine safety, ECT may allow us better treatment options for glioblastoma and other intracrainial malignancies.

2. MODERN ECT

Modern ECT is safe and effective in treating severe depressions that have not responded to standard medical treatment algorithms [2-5]. The American Psychiatric Association lists ECT during “conditions associated with increased intracrainial pressure such as [large] brain tumors”...as being “theoretically of great concern” [17] but also go on to say “Most reports of dire outcomes are from the distant past”...when wide blood pressure excursions were allowed to occur. We agree with these views.

Older ECT methods did not use general paralysis and cardiovascular stabilizing drugs that are now standard practice [6]. Many reports document safe and uneventful ECT in patients with intracranial aneurysms, tumors, and other states where an iatrogenic increase of intracranial pressure could be catastrophic [18-21]. In a recent review of the last decade of ECT use to treat psychiatric illness there were no ECT-related deaths in any VA [USA military veteran’s] hospital between 1999 and 2010 [18]. The estimated ECT-related mortality was less than 1 death per 73,440 treatments [18]. Morbidities found in this VA study were minor [18]. A single detail-poor case report of glioblastoma in an 80 year-old woman treated with ECT who did poorly post-ECT is of concern but difficult to evaluate or generalize upon [22] but this does warrant extreme caution in approaching this technique for better glioblastoma treatment. We must proceed carefully, on a basis of solid rodent study to establish safety likelihood. The current standard view in psychiatry and the American Psychiatric Association is that there are no absolute contraindications to ECT [4,14].

In ECT without neuromuscular blockade, as practiced in the first few decades after its introduction to clinical practice, hypoxia, hypercarbia, acidosis, and generalized clonic-tonic grand mal seizures were allowed to occur making earlier data on ECT difficult to compare to modern results where these phenomena are eliminated or minimized. Electroencephalographic signs of seizure remain identical to an un-medicated seizure [23, 24]. ECT can be given, albeit with some trepidation, to refractory depressed patients with intracrainial pathology that would make increases in blood pressure catastrophic, for example the case report of uneventful ECT course in a 54 year old woman with an unruptured 5 mm saccular basilar aneurysm [24].

3. ECT AND THE BBB

The recent remarkable finding of Zimmerman et al. [25] that peripheral blood beta amyloid levels [>4 kDa] increase after ECT, indicates robust BBB opening. Although circulating beta amyloid has not been considered a standard marker for BBB patency, we believe that Zimmerman et al. have given reason to reconsider this. ECT given for psychiatric indications was recognized as opening the BBB in 1977 [6], with a long history since then confirming this [27-29] yet also confirming no brain parenchyma damage occurs [28,30,31]. We have indirect MRI evidence of evanescent post-ECT increased brain water content as indirect

evidence of BBB loosening [32]. Ultrastructural and physiological characteristics of disrupted BBB function after ECT as well as after non-iatrogenic seizures was recognized in the 1980's [28,29]. Perhaps the most telling study to date showed T1 signal increasing after ECT, reaching a maximum 4-6 hour's post-ictally, returning to normal several hours later [28]. Together these reports indicate that a certain amount of post-ECT edema is occurring and should be of concern for our intended use of ECT in opening the BBB for better chemotherapy access to glioblastoma. But potential benefits may outweigh these risks. Only careful step-wise study can establish whether ECT can indeed be safely used in glioblastoma. The relentlessly reliable trajectory and short median overall survival in glioblastoma allows exploration of a disconcerting treatment process that at first seems counterintuitive. The Kierkegaard quote applies.

A bi-directional feed-back relationship exists between BBB leak and seizures. BBB leak promotes epileptogenesis and seizures while seizures promote opening of the BBB for several hours post-ictally [33-36]. Recognition of this reciprocal relationship [33,36,37] lead to the successful exploration of the antibiotics minocycline [38] and dapsone [39] as innovative and successful anti-seizure adjuncts by virtue of their anti-cytokine [40-42] and hence BBB tightening attributes. Similarly dexamethasone has anti-seizure properties by i.a. tightening the BBB [43]. BBB damage and inflammatory cytokine activation are both a consequence of seizure as well as being a predisposing or causal element of seizure generation [28, 34-37]. Reassuringly, repeated ECT as used in treating depression has been shown to not increase long term risk of epilepsy [44].

To not further complicate potential for intracrainial overpressure problems during use of ECT opening of the BBB, this should not be explored in the post-operative period but rather studied only after resection-induced edema has subsided and skin healed.

4. CONCLUSION

ECT may open the BBB enough to allow better chemotherapy access to the surgical cavity wall brain tissue wherein the centrifugally migrating glioblastoma cells reside. Due to post-ECT opening of BBB some post-ictal edema does occur and would be of concern for our intended use. Only study can establish the safety of this approach.

Considering giving ECT to open the BBB during chemotherapy of glioblastoma is not as radical as it at first sounds. In a study from the Mayo Clinic, eight patients with unrepaired abdominal aortic aneurysm were given ECT without incident or enlargement of their aneurysms [45]. Maltbie et al reviewed all published case reports of ECT delivered to patients with gliomas or metastases to brain up until 1980, finding high rates of deterioration after ECT [46]. As Maltbie et al's data was all from the pre-CT [and pre-MRI] era, and had space occupying malignancy we have grounds to consider modern post-resection ECT will be safer. Patkar et al. in 2000 reported an uneventful ECT course given to a 61 y/o man with an unresectable large left temporal astrocytoma with edema and mass effect [21]. Patker et al. in referring to older studies showing morbidity after ECT commented "None of these patients, however, received specific attention to diminish the ECT-associated risk" and that they felt proper pharmacologic attention to preventing increased intracranial pressure ECT can be safer than previously thought [21], a conclusion reached by others as well [47].

Given the reliably deadly progression of glioblastoma currently, study of an approach such as this is warranted, but on first look is disconcerting- we lose our footing somewhat. Recent

experience indicates that post-ECT edema in brain tumor patients can be managed. Case reports of successful and uneventful use of ECT in patients harboring brain tumors give cause for optimism. With small enough steps and careful pre-clinical study to assure no increase in intracrainial pressure can be achieved, further study of ECT as a new drug delivery modality can be undertaken.

CONSENT STATEMENT

This was a review of past research with presentation of a new method to open the blood-brain barrier based on that review. No patients or animals were involved.

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COMPETING INTERESTS

The authors have no conflicts of interest. This was unfunded research.

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