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Mystical Experience with Cancer Patients: Insights from Psychedelic-Assisted Psychotherapy and Guided Imagery

By Jerry B. Brown & Julie M. Brown

Abstract- Background: In controlled, clinical studies of the impact of psilocybin on patients with life-threatening cancers, Johns Hopkins and NYU researchers found that the “intensity of the mystical experience” induced by psychedelic-assisted psychotherapy was directly correlated with the alleviation of cancer-related mental distress.

Objective: The purpose of this article is to explore the proposition that the combination of psychotherapeutic guided imagery and psychedelic-assisted psychotherapy could not only alleviate cancer-related psychological distress but also reduce or eliminate physiological tumors.

Methods: The literature surrounding “mystical experience” is discussed; the modalities of psychedelic-assisted psychotherapy and guided imagery psychotherapy with cancer patients are compared; and the anecdotal outcomes of cancer remission among private therapy guided imagery patients are presented.

Keywords: cancer, mystical experience, neuroimaging, psilocybin, psychedelic-assisted psychotherapy.

GJMR-A Classification: NLMC Code: WM 420.5.P7
Mystical Experience with Cancer Patients: Insights from Psychedelic-Assisted Psychotherapy and Guided Imagery

Jerry B. Brown α & Julie M. Brown β

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Result: The following question is proposed for future research: can psychedelic-assisted psychotherapy augmented by guided imagery facilitate the reduction or elimination of tumors in cancer patients?

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In both trials, the intensity of the mystical experience described by patients correlated to the degree to which their depression and anxiety decreased.

-Johns Hopkins and NYU psilocybin-cancer studies

Introduction

Our contemporary understanding of the common elements in mystical experience is largely based on the ideas of William James (1902), The Varieties of Religious Experience, and Walter T. Stace (1961), Mysticism and Philosophy. These elements were refined, validated, and incorporated into a 30-question operational definition of mysticism, the Mystical Experience Questionnaire (MEQ30) utilized in the Johns Hopkins studies on the impact of psilocybin on reducing anxiety and depression in patients with life-threatening cancers (Barrett et al. 2015, MacLean et al. 2012).

The five common elements of mystical experience are:

1. Unity/Sacredness – deep sense of unity with all of existence; knowledge that "all is one"; profound sense of reverence.
2. Positive Mood/Ecstasy – deeply felt sense of well-being; experience of peace and tranquility; irrepressible feelings of joy and amazement.
3. Transcendence of Time and Space/Eternity – loss of usual sense of time and space; existing beyond past, present and future; entering a liminal, mythic dimension.
4. Authoritative/True Self – authoritative truth value of the experience (noetic); encounter with all-knowing presence; understanding one's authentic self.
5. Ineffable/Indescribable – difficulty describing the experience in words; impossibility of adequately communicating it to others.

I. Psychedelic-assisted Psychotherapy

Since 2006 the Johns Hopkins School of Medicine (Johns Hopkins) has been conducting the first research since the 1970s involving the administering of psilocybin to human subjects, including studies of personality changes and of psychedelic therapy for treating tobacco/nicotine addiction and cancer-related distress.

In 2016 Johns Hopkins undertook the largest ever study of psilocybin in treating chronic depression and anxiety among patients with life-threatening cancers. In this randomized, double-blind, cross-over trial, 51 patients were given a low placebo-like dose (1-3 mg/70 kg of body weight) vs. a high dose (22 or 30 mg/70 kg of body weight) in two sessions with six-month follow up. (Griffiths et al. 2016).

In a Journal of Psychopharmacology article, Roland R. Griffiths, Matthew W. Johnson, and colleagues report that “High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety” (Griffiths et al. 2016, p. 1). A six-month follow up study showed that these results were sustained in most of the participants.

Some 70 percent of the cancer patients rated the high-dose psilocybin sessions as among the top five...
“most meaningful” and “spiritually significant” life experiences. In addition, their post-session mystical experience scores served as statistically significant predictors of therapeutic efficiency in reducing anxiety and depression.


The daughter of one study participant noted that “This opportunity allowed my dad to have vigor in his last couple of weeks of life—vigor that one would think a dying man could not possibly demonstrate. His experience gave my father peace. His peace gives me strength” (Johnson 2018, slide 16). These outcomes prompted Griffiths to observe that “It’s very common for people who have profound mystical-type experiences to report very positive changes in attitudes about themselves, their lives, and their relationships with others.” And to exclaim, “To see people who are so beaten down by this illness, and they start actually providing reassurance to the people who love them most, telling them ‘it is all okay and there is no need to worry’—when a dying person can provide that type of clarity for their caretakers, even we researchers are left with a sense of wonder” (Schiffman 2016).

a) Guided Imagery-Assisted Psychotherapy

Julie M. Brown, coauthor of this article, is a retired psychotherapist who for twenty-five years specialized in helping cancer patients heal. In her private practice, she worked with a variety of therapeutic modalities, including guided imagery which she studied as a graduate student under her mentor in psycho synthesis.

Guided imagery, also known as visualization, is a technique through which psychotherapists help patients evoke and focus on mental images to facilitate relaxation, healing, and resolution of life issues. In guided imagery-assisted psychotherapy, a person calls on mental images to improve both emotional and physical health (see Samuels, 2003; Epstein, 1989).

This highlights an important distinction between psychedelic-assisted psychotherapy and guided imagery. The Johns Hopkins protocol is non-directive, simply encouraging study participants to “trust, let go and be open” and not providing instructions on where to focus. In contrast, the guided imagery modality is directive, with the therapist purposefully focusing patients to induce images and assisting in processing and integrating these images.

Often Brown’s cancer patients turned to psychotherapy after conventional treatment (chemotherapy, radiation, pharmaceuticals) failed to reduce or eliminate tumors. In the guided imagery sessions, Brown found that patients would at times enter states of mystical experience that empowered both emotional (anxiety, depression) and physical (cancer) self-healing.

b) Guided Imagery Therapy Outcomes

Between 1986 and 2011, Brown worked with 50 cancer patients, the majority of whom achieved full remission as evaluated by oncologists. The profiles and outcomes for three patients are summarized in this table.
Depending on the client’s situation, Brown frequently combined guided imagery in the context of psychotherapy with a complementary cancer approach. A complementary cancer approach may integrate a variety of tools including, but not limited to, emotional release work, breath work, nutrition, exercise, and meditation. This approach can help reduce the side effects of conventional treatment, improve client emotional and physical well-being, and enhance the healing process.

Unlike the controlled Johns Hopkins study involving 51 participants, Brown’s 50 case studies were neither validated by independent observers nor subjected to methodological controls – except for the patients’ cancer status which was monitored by their oncologists. Nevertheless, the seminal role of mystical experience in both psychedelic-assisted psychotherapy and guided imagery psychotherapy raises important questions.

c) Guided Imagery Questions for Future Research

In the case of Brown’s guided imagery outcomes with cancer patients, significant questions are:

- Can success in healing cancer utilizing guided imagery be replicated and validated? Beyond Brown’s anecdotal cancer outcomes have other therapists been able to reduce or eliminate tumors utilizing guided imagery? Could healing have taken place in this context without a complementary cancer approach, or was it the combination of this approach and guided imagery that facilitated remission?
- Can psychedelic therapy protocols be integrated into guided imagery therapy?

As a psychotherapist and a person with significant personal psychedelic experience, Brown hypothesizes that the ability to administer psilocybin to psychotherapy patients could conceivably shorten the healing process, possibly from years to months. Given that clinical trials on psilocybin for addressing major depression disorder have been granted “breakthrough therapy” designation by the U.S. Food and Drug Administration, what changes in state and federal policies, and in professional regulations, would have to take place so that psychiatrists and psychotherapists could legally integrate psychedelics into conventional treatment modalities?

d) Psychedelic Therapy Questions for Future Research

In the case of Johns Hopkins psychedelic therapy outcomes with cancer patients, significant questions are:

- Can psychedelic-assisted psychotherapy be used not only to alleviate psychological anxiety and depression in patients with life-threatening cancers, but also to facilitate physiological healing among cancer patients?

Given the pivotal role of mystical experience in both short-term psychedelic-assisted psychotherapy and long-term guided imagery psychotherapy, could psychedelic therapy combined with guided imagery possibly reduce or eliminate tumors in late-stage cancer patients?

- Will long-term, costly psychotherapy eventually be replaced by short-term, more affordable psychedelic-assisted psychotherapy?

Since short-term psychedelic therapy has achieved positive and sustained outcomes in 70 percent of the participants, based on one or two high-dose psilocybin sessions administered over several weeks, will it eventually replace, or significantly enhance, long-term psychiatric and psychotherapeutic modalities which require years of treatment and cost thousands of dollars?

II. Mystical Experience and Healing

It is well-established that mystical experiences have historically played a pivotal role in indigenous shamanism and world religions, such as the miracles
surrounding Moses’ burning bush and Jesus’ baptism (Brown and Brown, 2019; Brown and Brown, 2016; Winkelman, 2019). What is less well-known and quite unexpected is the discovery that mystical experiences are the catalyst for healing in contemporary psychedelic research.

Two studies of the impact of psilocybin on cancer patients, conducted at Johns Hopkins and NYU, found that “in both trials, the intensity of the mystical experience described by patients correlated with the degree to which their depression and anxiety decreased” (Hoffman 2016).

In other words, research scientists have reliably occasioned mystical experiences – “flights of the soul” traditionally thought to be beyond the scope of empirical science—in clinical settings by administering high-dose psilocybin. Furthermore, it turns out that these experiences hold the key to positive patient outcomes in psychedelic-assisted psychotherapy. Let this enigma sink in for a moment.

**a) Three Seminal Studies**

In the 1960s urban legends began circulating, claiming that psychedelics could allow intrepid trippers to meet spirit guides, to travel to other dimensions, and even to know God. In fact, the new science of psychedelics was in part inspired by the initiatory mystical experiences of early psychonauts: Stanislav Grof’s cosmic consciousness revelations on LSD in Prague (1993, pp. 15-16); Michael Harner’s near death journey on ayahuasca in the Amazon (1990, pp. 3-5); and Timothy Leary’s mind-expanding awakening on psilocybin mushrooms in Cuernavaca, Mexico (1960, pp. 11-34), to name but a few. Over time, the ability of psychedelics to generate authentic mystical experiences was confirmed by three seminal studies.

The first, the Miracle of Marsh Chapel (also called the “Good Friday Experiment”) was a psychedelic research experiment carried out by Walter N. Pahnke under the auspices of Leary’s Harvard Psilocybin Project. On Good Friday 1962, Pahnke randomly divided twenty volunteer Protestant divinity students into two groups assembled in a small room in the basement of Marsh Chapel on the campus of Boston University. In this controlled double-blind study, half the students received capsules containing thirty milligrams of psilocybin and the other half received a large dose of niacin (vitamin B3) as a placebo. The results were compelling. Almost all members of the group receiving psilocybin reported profound mystical experiences.

As Pahnke reports, “The persons who received psilocybin experienced to a greater extent than did the controls the phenomena described by our typology of mysticism” (Doblin 2012, p. 85). He built a follow-up survey into the research design, which found that six months after the experiment the psilocybin subjects reported persistent positive, and virtually no negative changes in their attitude and behavior.

The second study showed that the Good Friday Experiment could withstand the test of time and scrutiny by independent reviewers. A 25-year follow-up investigation conducted in 1987 by then-graduate student Rick Doblin, founder of the Multidisciplinary Association for Psychedelic Studies (MAPS), documented that “all seven psilocybin subjects participating in the long-term follow-up, but none of the controls, still considered their original experience to have had genuinely mystical elements and to have made a valuable contribution to their personal lives.” Doblin (2012, p. 87) concluded that Pahnke’s research on synthetic psilocybin “cast considerable doubt on the assertion that mystical experiences catalyzed by drugs are in any way inferior to nondrug mystical experiences.”

In assessing Pahnke’s research, Walter H. Clark, recipient of the American Psychological Association’s Award for contributions to the psychology of religion, states “There are no experiments known to me in the history of the scientific study of religion better designed or clearer in their conclusion than this one” (Doblin 2012, pp. 87-88).

A third round of studies, initiated more than 40 years after the Good Friday Experiment, was conducted at Johns Hopkins School of Medicine. In two papers, Griffiths and his colleagues empirically demonstrated that psilocybin could regularly result in mystical experiences with lasting benefits for participants (Griffiths et al. 2006; Griffiths et al. 2008). These double-blind studies found that: psilocybin was safe in structured, clinical settings; generated one of the five most meaningful life experiences for most participants; and produced improvements in mood and quality of life that were still present 14 months after the sessions.

**b) How Does Mystical Experience Facilitate Healing?**

The rigorous psychedelic therapy studies of stress reduction and the anecdotal guided imagery therapy cases of cancer remission described above suggest that mystical experience can facilitate both mental and physical healing. “How” this healing takes place is the theoretical Holy Grail of psychedelic-assisted psychotherapy.

Our quest to unravel this mystery begins with the insights of three mind explorers: Roland R. Griffiths, grandfather of the psychedelic renaissance; Robin Carhart-Harris, pioneer of psychedelic brain neuroimaging; and Carl G. Jung, who with Sigmund Freud laid the foundations of modern psychotherapy.

In essence, Griffiths observes that “the psilocybin experience enables a sense of deeper meaning, and an understanding that in the largest frame everything is fine and that there is nothing to be fearful of” (Schiffman 2016). How the brain expands from
ordinary consciousness to encompass this “largest frame” is visually revealed in Carhart-Harris’s functional magnetic resonance imaging (fMRI) of the brain’s neural pathways before and after ingesting psilocybin mushrooms.

### III. Brain’s Neural Pathways

Before and after Magic Mushrooms


Psychedelics allow us to leave the brain’s “default-mode network” (Carhart-Harris et al. 2014), the brain’s everyday information highway, and travel into areas of the mind accessible in non-ordinary states of consciousness, thereby creating a “superhighway to the unconscious” and access to mystical experience. In summarizing the findings of neuroimaging research with psychedelic drugs, Carhart-Harris (2014, p. 18) concludes, “Indeed, psychedelics greatest value may be as a remedy for ignorance of the unconscious mind.”

### IV. Inner Self-healing Intelligence

It is Jung’s (2017) “spiritual self” that embodies insights that emerge from the unconscious mind. Beyond Freud’s model, Jung proposes the existence of a “spiritual self,” also called “spiritual consciousness.” Through dreams, messages from the spiritual self are brought into awareness.

Mystical experiences arise when the doors of perception are flung wide open so that the spiritual self can surface from the depths of the psyche, empowering us to heal and understand that in the cosmic scheme of things “all is well.” As one of the pioneers of psychedelic psychotherapy, Stanislav Grof has guided over 3,000 LSD sessions. Based on his unparalleled experience with LSD and encyclopedic knowledge of the psychedelic literature, Grof (2019) observes that “Entering these [holotropic, transpersonal, mystical] states activates an inner self-healing intelligence, which automatically guides the process to unconscious material that has a strong emotional charge and is close to the threshold of consciousness. It then spontaneously brings this material to the surface for processing.”

In this context, it is worth noting that Grof has documented significant instances of auto-punitive emotions correlated with the emergence of cancer. In The Human Encounter with Death, he reported on research in which high dose LSD (200 to 600 micrograms) was given to terminally ill cancer patients (Grof and Halifax, 1977). In this study, Grof and associates at the Spring Grove State Hospital in Baltimore “…saw surprisingly frequent instances of severe guilt, feelings of self hatred, and autopunitive tendencies that had preceded the clinical manifestation of cancer by years or decades.” They also found that “It was not infrequent that cancer patients in their LSD
sessions saw direct links between such tendencies within themselves and their malignancies."

a) Can Positive Emotions Impact Immune Response?

To investigate the above findings from a medical perspective, it is essential to seek empirical evidence on the impact of mental states on healing cancer. It is important to go beyond the psychological phenomena of “mystical experience” and “inner self-healing intelligence” to determine if there is physiological evidence that positive emotions, such as those engendered by mystical experience, can significantly activate the body’s immune system.

Research conducted at the Faculty of Medicine at the Technion in Israel suggests that the prima facie answer to this question is “yes.” Studies of mouse models involving melanoma and lung cancer found that activation of the brain’s reward system helps regulate immune system function and enhances immune response (Ben-Shaanan, et. al. 2018). Specifically, activation of the dopamine-releasing neurons in the ventral tegmental area (VTA) of the brain significantly impacted tumors, resulting in a 46.5 percent reduction of tumor size after 14 days.

V. Conclusions

This paper shows that, in addition to appearing in dreams, the spiritual self may emerge through mystical experiences occasioned by psychedelic-assisted psychotherapy or evoked by guided imagery therapy. While controlled, clinical studies (n=51) at Johns Hopkins School of Medicine found that psychedelic-assisted psychotherapy alleviates anxiety, depression, and fear of death among patients with life-threatening cancers, anecdotal observations (n=50) among cancer patients being treated in private practice found that guided imagery psychotherapy reduces or eliminates tumors among advanced stage cancer patients. Based on these observations, the following question is proposed for future research: can psychedelic-assisted psychotherapy augmented by guided imagery facilitate the reduction or elimination of tumors in cancer patients?

Hopefully, these reflections on the role of mystical experience in psychotherapy will inspire further exploration of this unique phenomena that holds a key to healing and well-being.

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Conflict of interest

The coauthors have no conflicts of interest neither in writing this article nor regarding the subject matter of this article.

References Références Referencias

Mystical Experience with Cancer Patients: Insights from Psychedelic-Assisted Psychotherapy and Guided Imagery

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Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer’s Disease

By Vic Shao-Chih Chiang

University College London

Abstract- The mitochondria are the powerhouses of the body, which is paramount for the central nervous system given their high energy expenditure. This high dependence on the mitochondria renders mitochondrial dysfunctions to impair the central nervous system, as seen in neurodegenerative diseases. This article concentrates on the neurodegenerative disease, Alzheimer’s disease and the well-established neuroinflammation pathophysiology, from a mitochondrial perspective. I first focused on the energy production functions of the mitochondria, and the mitochondrial DNA, imperative for mitochondrial function. For instance in their aberrations in Alzheimer’s disease, and in vitro experiments with inflammatory markers that drove damages to the mitochondria DNA. Subsequently, I discussed about mitochondrial biogenesis using expression studies with correlated changes in Alzheimer’s disease and stem cells whereby mitochondria are critical regulators of their fate, pertinent to Alzheimer’s disease. Finally, I accentuated on emerging technologies that enable disentangling the abstruse nature of mitochondria, and some uprising areas of mitochondria research deserving attention from the lens of Alzheimer’s disease. Overall, there is a plausible link between Alzheimer’s disease, neuroinflammation, and mitochondrial mechanisms, but current studies are limited to causally address this question. I presented several improvements and strategies that could be taken to advance the understanding of this relationship in future studies.

GJMR-A Classification: NLMC Code: WW 400
Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer’s Disease

Neuroinflammation affects Mitochondrial Function

Vic Shao-Chih Chiang

Abstract: The mitochondria are the powerhouses of the body, which is paramount for the central nervous system given their high energy expenditure. This high dependence on the mitochondria renders mitochondrial dysfunctions to impair the central nervous system, as seen in neurodegenerative diseases. This article concentrates on the neurodegenerative disease, Alzheimer’s disease and the well-established neuroinflammation pathophysiology, from a mitochondrial perspective. I first focused on the energy production functions of the mitochondria, and the mitochondrial DNA, imperative for mitochondrial function. For instance in their aberrations in neuroinflammation pathophysiology, from a mitochondrial perspective. I first focused on the energy production functions of the mitochondria, and the mitochondrial DNA, imperative for mitochondrial function. For instance in their aberrations in mitochondria, and the mitochondrial DNA, imperative for mitochondrial function. For instance in their aberrations in Alzheimer's disease, and in vitro experiments with inflammatory markers that drove damages to the mitochondria DNA. Subsequently, I discussed about mitochondrial biogenesis using expression studies with correlated changes in Alzheimer's disease and stem cells whereby mitochondria are critical regulators of their fate, pertinent to Alzheimer's disease. Finally, I accentuated on emerging technologies that enable disentangling the abstruse nature of mitochondria, and some uprising areas of mitochondria research deserving attention from the lens of Alzheimer's disease. Overall, there is a plausible link between Alzheimer’s disease, neuroinflammation, and mitochondrial mechanisms, but current studies are limited to causally address this question. I presented several improvements and strategies that could be taken to advance the understanding of this relationship in future studies.

I. INTRODUCTION

Mitochondria are 0.5 – 1.0 μm cellular organelles that generate energy in the form of ATP. By virtue of the high energy expenditure in the central nervous system, mitochondria pose exceptionally important roles. Corresponding to their gravity, multiple neurodegenerative diseases exhibit mitochondrial dysfunction. Alongside mitochondrial dysfunction, neurodegenerative diseases frequently accompany chronic inflammation within the brain. Scholars termed this as “neuroinflammation” and while this phenomenon serves a diverse range of purposes, it most fundamentally associates with the body’s natural innate immune response to eliminate unwanted material and initiate repair. Is there a relationship between neuroinflammation and mitochondrial function? Could neuroinflammation be the cause of mitochondrial dysfunction? To answer this, this article concentrates on sporadic Alzheimer’s disease (AD) due to decades of research since the 1970s that supports a role of inflammation in AD pathophysiology. AD is a disease that leads to progressive synaptic degeneration and neuronal death with ageing. In the US, researchers estimated the prevalence of AD to affect one in three elders and ascribed to a financial burden estimated to be well over $200 billion. This article aims to answer whether neuroinflammation may affect mitochondrial function in the context of AD in relation to three fundamental aspects of mitochondrial function: mitochondrial energy production, mitochondrial DNA, and mitochondrial biogenesis.

II. NEUROINFLAMMATION MAY AFFECT MITOCOCHONDRIAL ENERGY PRODUCTION

Mitochondria is the critical site of energy production through the tricarboxylic acid cycle and oxidative phosphorylation (OXPHOS) during respiration. In particular, OXPHOS generates a large amount of energy in the form of ATP by electron transfer from NADH and FADH2 in the electron transport chain. Respiration and OXPHOS energy production are disrupted in AD (Table 2). Ageing studies were included in Table 2 to provide further insights since ageing is the greatest risk factor for neurodegeneration. From this, OXPHOS and respiration appear to reduce with AD and ageing. In saying that, these studies deployed animal models, which deviates from human AD progression, ergo, researchers should attend to possible caveats of clinical translatability. Aside from the differences reported, some of these animal studies have also provided results for other components of the electron transport chain. However, these failed to demonstrate any differences compared to the control. The failure of global changes in these components can create a selection bias where researchers make interpretations only on the OXPHOS components they selected to measure. Respiration is an objective measure for energy production. Therefore, future studies should include...
incorporating respiration as the primary outcome to reduce ambiguity in interpretation. Researchers can then further investigate these differences in respiration which specific components of the electron transport chain may drive this. Two reviews have summarized older studies that have consistently demonstrated that inflammatory cues affected respiration\cite{21,22}. One study focused on how NO inhibits respiration in neurons due to NO restriction of complex I \cite{21}. Another review concentrated on sepsis, which is the acute systemic inflammation from exposure to bacterial endotoxins (e.g., lipopolysaccharide LPS)\cite{22}. It summarizes clinical, animal, and cellular studies and provides countenance to the view for reduced respiration, ATP/ADP ratio, and protein expression of OXPHOS complexes during sepsis\cite{22}. Two other studies not covered in these reviews tendered supplementary support that inflammation does affect measurements relevant to mitochondrial energy production. The LPS treatment of murine macrophages (B6-MCL) and bone marrow-derived macrophages resulted in the complex IV gene and protein expression increase\cite{23}. In tandem with this, another study espoused this relationship in the context of feeding different lipid-based diets to overweight subjects\cite{24}. The comparing diets developed differences in pro-inflammatory proteins in the plasma, including IL1\(\beta\), macrophage inflammatory protein 1\(\alpha\), and serum amyloid P\cite{24}. Surprisingly, with the decrease in plasma inflammatory proteins, their microarray data showed down-regulation of various OXPHOS-related genes in the peripheral blood mononuclear cells of these subjects\cite{24}. These studies present evidence that inflammation may affect mitochondrial energy production. Notwithstanding, their results displayed opposing views regarding how it perturbed mitochondrial energy production. On the grounds that these researchers did not undertake further experiments to disentangle the mechanisms for these observations, it is imperative to enunciate a more solid framework to construe the data. For example, reduced energy production may not always be inimical, such that it may reduce the amount of oxidative stress\cite{24}. It would be context-dependent whether changes in mitochondrial energy production are deduced as beneficial or adverse. Likewise to the abovementioned, future studies should consider respiration as the primary outcome to reduce the indefiniteness of any speculations. In addition to that, by virtues of cell and tissue-specificity most probable for the effects of inflammation on mitochondrial energy production, future research in this domain specific for AD is warranted. Neuroinflammation likely affects mitochondrial energy production, but its existence in circumstances of neurodegeneration awaits discovery.

III. **Neuroinflammation may affect mitochondrial DNA**

Mitochondria possess DNA (mtDNA), and unlike nuclear DNA, it transcribes and replicates outside of the cell cycle\cite{25}. Due to the mtDNA encoding for pivotal proteins for the mitochondria, any adverse changes to this DNA may subsequently develop the impaired mitochondrial function\cite{25}. AD unerringly leads to changes in the mtDNA content and increases the number of mutations (Table 2). Single mitochondrion may contain multiple mtDNA, and single cells contain multiple mitochondria. The multiple mtDNA and mitochondria put the cells at risk of heteroplasmy, which refers to the presence of heterogeneous mtDNA within the same cell\cite{26}. Mutations present in heterogeneous mtDNA may gain power through clonal expansion that can occur rapidly independent of the cell cycle\cite{26}. Accumulation of adverse mtDNA mutations may compromise mitochondrial functions. Further to this, mtDNA changes appear to be site-specific\cite{27}, henceforth future studies should demarcate the most vulnerable sites to determine therapeutic priorities. Only a paucity of studies exists which examines how inflammation may directly affect mtDNA. Researchers identified using TNF\(\alpha\) and IL1\(\beta\) treatments in primary human chondrocytes to increase mtDNA breaks\cite{28}. Germane to this alludes to a study utilizing primary murine peritoneal macrophages\cite{29}. They observed LPS translocating mtDNA into the cytoplasm through unknown interactions with the cryopyrin inflammasome\cite{29}. The authors speculated this as adverse on the grounds that the loss of mtDNA from the mitochondria could debilitate mitochondrial function\cite{29}. These limited data are adjuvant to the notion that inflammation may affect mtDNA. However, substantially more studies are required to ascertain this effect, especially those relevant to the central nervous system. Major drawbacks with these studies lie in their insufficient exploration of the mtDNA. For example, future studies should recognize the importance of identifying heteroplasmy and specific types of mtDNA breaks or mutations that ensue with inflammation. MtDNA demonstrated the possibility to be affected by neuroinflammation, but whether this is present in the central nervous system remains to be explored.

IV. **Neuroinflammation may affect mitochondrial biogenesis**

Mitochondria are constantly undergoing turnover to replace damaged mitochondria with functional counterparts\cite{18}. The process of generating new mitochondria is termed “mitochondrial biogenesis”\cite{18}. Disruptions to this process may affect the number of mitochondria available to carry out paramount cellular functions. The homeostasis of mitochondrial biogenesis
appeared to be disturbed in AD (Table 3), evident in the overall reduction of gene and protein expression related to mitochondrial biogenesis. However, this trend contrasts with this study\textsuperscript{30}, where researchers found mitochondrial biogenesis to increase in AD. This study experimented with primary hippocampal neurons derived from the Tg2576 AD mouse model in comparison to those that originated from wild-type mice\textsuperscript{30}. They further subjected these neurons to oxidative stress to exacerbating neurodegeneration\textsuperscript{30}. Based on their bromodeoxyuridine labelling, they unearthed an increase in mitochondrial biogenesis\textsuperscript{30}. Their explanation for this contingent finding was the mtDNA of these neurons had a reduced half-life, which reciprocally stimulated additional mitochondrial biogenesis \textsuperscript{30}. From this, I hypothesize that impairments in mtDNA may precede dysfunctional mitochondrial biogenesis. The initial compensation to counteract detrimental effects from impaired mtDNA through intensifying mitochondrial biogenesis may also become dysfunctional at later stages of AD. Could neuroinflammation affect mitochondrial biogenesis? We can take clues from hypoxia studies as NO is generated\textsuperscript{31}. Mice subjected to hypoxia had increased gene expression of PGC1\textalpha, NRF1, and TFAM within their brains\textsuperscript{31}. Additionally, with the observed strengthening of mitochondrial density in their brains, researchers inferred that mitochondrial biogenesis augmented\textsuperscript{31}. This effect was known to be directed by NO since changes in mitochondrial biogenesis were absent in neuronal and endothelial NO synthase gene-deficient mice\textsuperscript{31}. Other studies of the central nervous system detected simultaneous changes in inflammation and mitochondrial biogenesis (↑ plasma chemokine ligand 11 protein, ↑ PGC1\textalpha protein\textsuperscript{32}, ↓ brain NF\textkappaB: chemokine ligand 11 genes, ↑ PGC1\textalpha, NRF1, TFAM\textsuperscript{33}). However, the researchers did not further correlate these variables in these studies. Several other studies likewise support the notion that inflammation affects mitochondrial biogenesis, albeit not in the central nervous system. A good illustration exemplifies in a study that treated human cardiac AC16 cells with TNF\textalpha\textsuperscript{34}. This experiment resulted in the down-regulation of PGC1\textalpha protein expression\textsuperscript{34}. Furthermore, LPS treatment of human gingival fibroblasts diminished protein expressions of PGC1\textalpha and TFAM\textsuperscript{35}. Another example was the human knee chondrocyte study carried out by \textsuperscript{36} that found IL1\beta treatment to reduce protein levels of PGC1\textalpha, TFAM, NRF1, and NRF2. From these studies, it can be asserted that neuroinflammation affects mitochondrial biogenesis. However, it remains equivocal whether mitochondrial biogenesis is increased or decreased with inflammation. It is imperative to consider the inflammatory mediators utilised in these studies as their effects on mitochondrial biogenesis may be distinct from each other. Neuroinflammation involves a plethora of inflammatory mediators, and therefore, the synergistic or antagonistic effects on mitochondrial biogenesis from different combinations require to be elucidated. In vivo AD studies of chronic inflammation are similarly sine qua non to address the drawbacks of existing studies on inflammation and mitochondrial biogenesis. Neuroinflammation affects mitochondrial biogenesis, but elaborate substantiation in in vivo AD studies awaits.

V. Neuroinflammation and Mitochondria in the Context of Stem Cells

Memory is impaired in AD patients, which correlates with hippocampal degeneration, a site imperative for adult neurogenesis (reviewed in \textsuperscript{37}). Supporting clinical evidence espouse abated neurogenesis in AD patients (reviewed in \textsuperscript{38}). In several rodent studies, amelioration of the AD sequelae oftentimes accompanies rescued neurogenesis (reviewed in \textsuperscript{37}). For example, in an immunotherapy study, the successful delivery of antibody therapeutics across the blood-brain barrier promoted hippocampal neurogenesis\textsuperscript{38}. Another study enabling better causal inference, directly administered mesenchymal stem cells, which can differentiate into neuronal-like cells, demonstrated reversal of aberrant signalling pathways related to AD \textit{in vitro} \textsuperscript{39} and in 3x Tg-AD mice model \textsuperscript{40}. Given that the mitochondria are key signalling organelles for stem cell fate (reviewed in \textsuperscript{41}), it is highly plausible that the observed changes in AD symptomatology may mediate through the mitochondria. For instance, stem cell fates may be controlled through the mitochondria by generating reactive oxygenspecies (ROS), influencing bioenergetics, as well as mitochondrial dynamics (reviewed in \textsuperscript{41}). Particularly relevant to AD are neural stem cells and ample evidence likewise buttress mitochondrial regulation through affecting their proliferation, daughter cells, and transcriptional changes especially through mitochondria metabolism (reviewed in \textsuperscript{42}). Several of the mitochondrial components involved have been mentioned above to be altered by neuroinflammation. For instance, ROS increases neural stem cell self-renewal \textsuperscript{43} and with correlative evidence, scholars have postulated NLRP3 inflammasome to modify mitochondrial ROS production \textsuperscript{44}. Mitofusin-2 is a pivotal component in mitochondrial dynamics, and essential for the differentiation of induced pluripotent stem cells into cortical neurons \textsuperscript{45}. Recently, transgenic mice overexpressing mitofusin-2 demonstrated its critical roles in response to LPS-induced neuroinflammation \textsuperscript{46}. In essence, I hypothesize the mitochondria to mediate the effects of stem cell changes in AD through neuroinflammation mechanisms, which require vindication with mechanistic \textit{in vivo} studies.
VI. Technology to Study Neuroinflammation effects on Mitochondria

In order to rigorously obtain scientifically valid data to answer the plethora of experimental questions described throughout this review, the methodology deployed is the perforce consideration factor. Methods for studying the mitochondria has advanced dramatically over the past few decades from studying their morphology and metabolism to their physical properties. First, the three-dimensional ultrastructure of the mitochondria requires resolution through electron microscopy (reviewed in 47). However, traditional methods of manual segmentation of mitochondria imaging in electron micrographs become rate-limiting in the contemporary data-driven era (reviewed in 47). Therefore a recent study utilized machine learning in the form of a recurrent neural network to enable automated detection and segmentation of the electron micrographed mitochondria47. To conduct analysis beyond visualization, isolating the mitochondria is a pivotal method for detailed molecular examination. Several methods exist for this purpose that has varying success with regards to the number of mitochondria retained and preservation of membrane integrity (reviewed in 48). One study compared between three different methods, and ferreted out there was no superiority of one method, but each method harboured different strengths, either having a higher yield of mitochondrial protein and mtDNA copy numbers, higher activity retained in the isolated mitochondria or better membrane integrity 48. Ergo, researchers were recommended to carefully assess which methods most suit them depending on the purpose of their research. As mentioned previously, mitochondrial ROS has tremendous implications in Alzheimer’s disease. There have been endeavours of measuring mitochondrial ROS using redox-active probes, but these were limited due to the probe oxidation by several ROS (reviewed in 49). One study implemented an electron paramagnetic resonance approach that enabled overcoming this hurdle to identify specific ROS generated 49. Another challenge with ROS is their short lifetimes and high reactivity (reviewed in 50). One recent solution employed relaxometry from field magnetometry achieved quantum sensing of ROS at the mitochondrial resolution 50. A myriad of methods is commensurately materializing to understand the physics associated with mitochondria. To name a few, an emission probe was developed to monitor mitochondrial viscosity, cardinal for understanding damaged mitochondria51, as well as a molecular thermometer to measure the temperature in mitochondria, which impart information on cellular inflammation52. Above all, we are at a time where exciting avenues of mitochondria research could be sought through the advancements in vanguard methods to dissect the wonders of the mitochondria.

VII. Future Directions

Beyond the AD topics discussed in the review in the context of mitochondria and neuroinflammation, a myriad of emanating areas of the mitochondria require to be unearthed for their potential in AD pathophysiology. For example, the TCA cycle in the mitochondria generate metabolites for epigenetic mechanisms, yet it was only recently discovered the exigent impact of mitochondria on epigenetics (reviewed in 53). Another area that is beginning to recognize mitochondria as new players is firing rate homeostasis that stabilizes neural circuit function by maintaining firing rate distribution among neurons 54. The authors laid out cogent arguments for the mitochondria as part of this homeostatic machinery using robust theoretical frameworks 55. Vis-à-vis AD, indeed several studies endorsed the claim of an impaired firing homeostatic control in AD. These studies were conglomered in two articles led by Inna Slutsky whereby a dysregulated integrated homeostatic network may drive causations in AD progression at its early stages (reviewed in 56, reviewed in 57). The final uprising area in mitochondria research I want to accentuate is gut microbiota. In one study through trans-kingdom network analysis, mitochondria in the liver exhibited improved metabolism through metabolites derived from the Lactobacillus genus 58. Another study leveraged blood and faecal samples found correlations between mitochondria-related inflammation with the Lachnospiraceae family, amongst other findings 59. This intersects with the role of gut microbiota in AD pathogenesis, that have already garnered a gargantuan amount of attention in the past decade (reviewed 59). There are an abound of approaches that strive to implement these insights into AD treatments such as using faecal microbial transplants (reviewed 59). In saying that, the efficacy and safety of these treatments remain to be conclusively grasped, and understanding the role of mitochondria in their effects is crucial for this endeavour. As can be seen, a variety of novel areas in mitochondria research are being developed. The intersection of these areas of epigenetics, firing rate homeostasis, and gut microbiota with AD, indicate ripeness of exploring these in the crossover between AD, neuroinflammation, and mitochondria.

VIII. Conclusion

Sporadic Alzheimer’s disease is under a chronic state of neuroinflammation. Simultaneously, AD patients exhibit signs of mitochondrial dysfunction. Their
Mitochondria have a reduced capacity to carry out energy production. In addition, increased mutations in their mitochondrial DNA could impair the transcription of components for mitochondrial function. These are in conjunction with disturbed homeostasis of molecular components required for mitochondrial biogenesis. Altogether, these may be culprits for altered stem cell fates that goads AD pathophysiology. This article answers whether the neuroinflammation in AD may be responsible for the observed mitochondrial dysfunction. However, I raised more questions than answers due to the limited amount of data available and the substantial amount of research still required. Although limited, existing data supports neuroinflammation to affect mitochondrial energy production, mitochondrial DNA, and mitochondrial biogenesis. To answer this question conclusively, we need future in vivo central nervous system studies in the context of AD, using the emerging technologies I described. These studies should generate primary outcomes that minimize the possibility of any ambiguity in interpretation. Other measurements taken must spread in breadth and depth to correspond to mitochondrial dysfunction data in AD patients. In tandem with these, researchers must account for the complexity of neuroinflammation demands in their experimental design, and emphasize the potential of emerging areas in epigenetics, firing rate homeostasis, and gut microbiota. AD is a highly prevalent disease that contributes to an immense societal burden. Understanding how the underlying neuroinflammation contributes to AD could help develop novel or improved strategies to combat this.

Conflict of interest
The author declares no conflict of interest.

Table 1: Changes in mitochondrial OXPHOS and respiration in Alzheimer's disease and ageing

<table>
<thead>
<tr>
<th>Study Sample</th>
<th>Sample Type</th>
<th>Changes in OXPHOS / respiration (methodology of assessment)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Wistar Rats (20 months)</td>
<td>Hippocampus</td>
<td>□ ↓ state 3 respiration (initiated with ADP) (Clark electrode)</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ↓ Complex I &amp; IV activity (spectrophotometry)</td>
<td></td>
</tr>
<tr>
<td>Female triple transgenic AD mice (3xTg-AD)</td>
<td>Hippocampus</td>
<td>□ ↓ mitochondrial respiration (Clark electrode)</td>
<td>62</td>
</tr>
<tr>
<td>(3 months)</td>
<td></td>
<td>□ ↓ mitochondrial respiration (Seahorse XF-24 metabolic flux)</td>
<td></td>
</tr>
<tr>
<td>Male Wistar rats (30 months)</td>
<td>Cortex</td>
<td>□ ↓ ATP synthase (1D-SDS gel)</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ↓ Complex I (1D BN-gel &amp; 2D SDS-gel)</td>
<td></td>
</tr>
<tr>
<td>Male Wistar rats (24 months)</td>
<td>Brain</td>
<td>□ ↓ Complex I activity (mitochondrial particles)</td>
<td>64</td>
</tr>
<tr>
<td>APPswe/PS1dE9 mice (3 months)</td>
<td>Hippocampus</td>
<td>□ ↓ state 3 respiration (initiated with ADP) (Clark electrode)</td>
<td>65</td>
</tr>
<tr>
<td>Female Wistar rats (24 months)</td>
<td>Hippocampus, cortex, cerebellum,</td>
<td>□ ↓ Complex I, II, III, IV activity (spectrophotometry)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>brainstem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMRI-mice (24 months)</td>
<td>Frontal brain region</td>
<td>□ ↓ Complex I, II, IV activity (respirometer)</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ↓ ATP levels (bioluminescence)</td>
<td></td>
</tr>
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</table>
### Table 2: Changes in mitochondrial DNA in Alzheimer’s disease and ageing

<table>
<thead>
<tr>
<th>Study Sample</th>
<th>Sample Type</th>
<th>Changes in mitochondrial DNA (methodology of assessment)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD patients (76.3 yrs)</td>
<td>Hippocampal pyramidal neurons</td>
<td>□ †total mtDNA deletions (qPCR N4:N1)</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ † size &amp; † number of mtDNA deletion break points (long extension PCR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ † “common” &amp; “major arc” mtDNA deletions (Sequencing)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ † single nucleotide variants (Sequencing)</td>
<td></td>
</tr>
<tr>
<td>Caucasian male (67 - 89 yrs)</td>
<td>Putamen</td>
<td>□ † m.3243A&gt;G tRNA mutation (Sequencing)</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ † clonal ~50bp deletions in the control region (Sequencing)</td>
<td></td>
</tr>
<tr>
<td>Male Fischer 344 rats (26 months old)</td>
<td>Frontal cortex</td>
<td>□ 25% ↓ in mtDNA content (qPCR D-loop: β-actin)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 37% ↑ in 4.8kb deletions (qPCR 4.8kb deleted region: D-loop)</td>
<td></td>
</tr>
<tr>
<td>AD patients (56 - 86 yrs)</td>
<td>Different brain sections</td>
<td>□ † mtDNA deletion in cerebellar granule cells &gt; pyramidal cells (qPCR N4:N1)</td>
<td>27</td>
</tr>
<tr>
<td>AD patients (59 - 93 yrs)</td>
<td>Frontal cortex</td>
<td>□ ↓ mtDNA content (qPCR ND2: 18S rRNA)</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ↑ heteroplasmy (Sequencing)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ ↑ T414G mutation (PNA-clamping PCR)</td>
<td></td>
</tr>
<tr>
<td>AD patients (65 - 90 yrs)</td>
<td>Blood</td>
<td>□ ↑ heteroplasmy (sequencing &amp; PCR)</td>
<td>72</td>
</tr>
</tbody>
</table>

qPCR, quantitative real-time polymerase chain reaction

### Table 3: Changes in mitochondrial biogenesis in Alzheimer’s disease and ageing.

<table>
<thead>
<tr>
<th>Study sample</th>
<th>Sample type</th>
<th>Changes in mitochondrial biogenesis</th>
<th>Method of assessment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Fischer 344 rats (24 - 28 months)</td>
<td>Livers</td>
<td>↓ nuclear Nrf2 protein expression</td>
<td>Western blotting</td>
<td>73</td>
</tr>
<tr>
<td>AD patients</td>
<td>Hippocampus</td>
<td>↓ PGC1α gene expression</td>
<td>Microarray &amp; qPCR</td>
<td>74</td>
</tr>
<tr>
<td>Female Wistar rats (24 months)</td>
<td>heart, lung, liver</td>
<td>↓ intracellular NAD+ &amp; NAD: NADH ratio (sirtuin 1 substrate – regulates PGC1α)</td>
<td>Thiazolyl blue microcycling assay</td>
<td>75</td>
</tr>
<tr>
<td>AD Mice model (Tg2576 line)</td>
<td>Primary hippocampal neurons (treated with rotenone &amp; H2O2)</td>
<td>↑ mitochondrial biogenesis</td>
<td>BrdU labeling</td>
<td>30</td>
</tr>
<tr>
<td>AD patients (65 - 91 yrs)</td>
<td>Hippocampus</td>
<td>↓ protein expression of PGC1α, NRF1/2 &amp; TFAM</td>
<td>Western blotting</td>
<td>76</td>
</tr>
<tr>
<td>AD Mice model (APPswe/PS1dE9)</td>
<td>Brain</td>
<td>↓ PGC1α gene expression</td>
<td>qPCR</td>
<td>65</td>
</tr>
</tbody>
</table>

Bromodeoxyuridine, BrdU; mitochondrial transcription factor A, TFAM; nicotinamide adenine dinucleotide, NAD; nuclear respiratory factor, NRF; peroxisome proliferated-activated receptor gamma co-activator one alpha, PGC1α; quantitative real-time polymerase chain reaction, qPCR
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Rare Case of Young Patient with Intraventricular Angiomatous Meningioma

By Gabriel Carvalho Heemann, Vinicius Rosa de Castro, Normando Guedes Pereira Neto, Camila Bocchi, Otavio Garcia Martins, Rafael Silva Paglioli & Ricardo Chmelnistky Wainberg

Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul

Abstract- Pediatric meningiomas are rare and account for only 2.2% of CNS tumors. In this age group, they are more frequently located in atypical sites, such as, mainly, the ventricular system, with a frequency of 8.8 to 13.6%. Adding this to the fact that the angiomatous subtype constitutes only 2.1% of all meningiomas, the rarity of the case reported here is corroborated. We report a 17-year-old female patient diagnosed with intraventricular angiomatous meningioma; she underwent surgical resection of the tumor in the body and frontal horn of the right lateral ventricle, and there was no neurological sequela. With a follow-up of 4 years, there was no recurrence and the patient had clinical stability. Intraventricular tumors usually have slow growth and reach considerable size until they cause symptoms and then are diagnosed. In addition, the tumor’s deep location and proximity to eloquent areas make such tumors a neurosurgical challenge. The angiomatous subtype, due to the presence of hypervascularization (consisting of more than 50% of vascular components), may, in some cases, hinder surgical resection as well as be erroneously diagnosed. However, surgical treatment aimed at total resection of the lesion remains the conduct of choice in the case reported here, especially in patients in the first two decades of life, in which the use of radiation is avoided. Specifically when it comes to the surgery, we chose a transcallosal approach that allows a good transoperative visualization of the lesion when located in the body and frontal horn of the lateral ventricle.

GJMR-A Classification: NLMC Code: WL 140

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I. Introduction

Meningiomas have a progressively higher incidence with increasing age, with a mean age of presentation of 65 years. They are, therefore, the most frequently reported tumors of the central nervous system (CNS) in adulthood. However, cases in children and adolescents are rare, representing 2.2 to 2.6% of CNS tumors. In such age group, are more often located in unusual sites, such as in the ventricular system.

Such intraventricular meningiomas have the particularity of being slow growing and reaching considerable size until they become symptomatic. In addition, the deep location and relationship with underlying eloquent areas make tumor resection a neurosurgical challenge. In view of this, and that the angiomatous subtype—defined as presenting more than 50% of vascular components on microscopic analysis—constitutes only 2.1% of all meningiomas, rarity is credited to the case reported here. We emphasize that this is possibly the first report of a patient in the first two decades of life with angiomatous meningioma in an intraventricular site.

In this report, we aim to expose our neurosurgical experience in a case with rare variants and perform a literature review on the main aspects that we deem necessary to support our approach.

II. Case Report

A 17-year-old female patient, previously healthy, presented retro-orbital headache for 3 months, followed by blurred vision and double vision. Physical examination revealed just a convergent strabismus due to paresis of the right lateral rectus muscle. The cranial magnetic resonance (MRI) showed an expansive lesion in the frontal horn of the right ventricle, just in front of the foramen of Monro, with dimensions of 2.0 x 1.3 x 1.8 cm (AP x L x h) in the larger diameter cuts.

The lesion presented moderate hyperintensity with small hypointense foci on T2-weighted images. On T1, it was isointense, and after contrast, it showed intense and homogeneous uptake, except in the same hypointense foci on T2. There were no signs of dilation of the supratentorial ventricular system (Fig. 1 A - D). Such radiological characteristics suggested the diagnosis of intraventricular meningioma, with areas of calcification. It was considered an occasional finding, since the topography was not compatible with the presenting symptoms.

The surgical treatment was performed in the same hospitalization, due to the risk of acute hydrocephalus. The approach was made via the transcallosal route, following the steps: dorsal decubitus and head in a neutral position; bicoronal incision; right frontal paramedian craniotomy, with lateral extension of 5.5 cm from the midline and 5.5 cm from the coronal suture forward; opening the dura mater in a “C” shape, with the base facing the midline; under microscopy, dissection of the inter-hemispheric fissure and retraction of the frontal lobe with placement of the fixed spatula (on a Leyla support) on the medial surface; identification of the cingulate gyrus and pericallosal arteries; callosotomy with 1.2 cm starting from the transition between the knee and the corpus callosum; identified a grayish vegetating lesion inside the right frontal horn,

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which had a soft consistency and were vascularized; resection of the lesion through coagulation and aspiration and by fragments, leaving a small residue adhered to the ependyma of the caudothalamic groove. Postoperatively uneventful and absence of new deficits, with diplopia and strabismus remaining.

Histopathological analysis and immunohistochemical panel showed extensive vascularization and low mitotic index (Ki67 less than 2%). In addition, that results were visualized: epithelial membrane antigen (EMA), positive; cytokeratin (CK), negative; progesterone receptor, negative; and glial fibrillary acidic protein (GFAP), positive (Fig.2 A-B). Thus, the diagnosis of angiomatous meningioma (WHO grade I) was confirmed. Postoperative MRI showed a small residual focus near the thalamostriate groove (Fig. 3 A-D and Fig. 4 A-D). After 6 months, the patient underwent strabismus correction with an ophthalmologist at another institution. Currently, with approximately 4 years of follow-up, she is asymptomatic and without evidence of recurrence of the residual lesion.

III. Discussion

Meningiomas are tumors that predominate in the fifth and sixth decades of life, with a mean age of presentation of 65 years. In general, they represent 36.4% of primary CNS tumors and approximately 24-30% in adults. Nevertheless, in the pediatric population, the prevalence among CNS tumors varies between 0.4 and 4.6%. The equivalence between genders also contrasts with what occurs in the adult population, which has a female to male ratio of 2:1. This difference is believed to be due, mainly in the prepupalateral, to the absence of the effect of sex hormones on corticosteroid receptors in meningioma cells.

In the first two decades of life, there is a higher incidence of grade II (atypical) and grade III (anaplastic) meningiomas, according to the WHO: 9.9 and 8.9%, respectively. They are genetically and phenotypically more aggressive with a high frequency of brain invasion. Among the most frequent grade I meningiomas, the angiomatous subtype occurs in 2.8% of cases, and in 2.1% of all meningiomas at any age. Such subtype is defined when the vascular component exceeds 50% of the total area of the tumor. However, the differential diagnosis with hemangioblastoma and hemangiopericytoma is necessary, with immunohistochemistry and morphology having essential roles in the diagnostic confirmation: low MIB-1/Ki67 index and positivity for progesterone receptor, EMA, vimentin, cytokeratin, and desmoplaquin.

The characteristics of angiomatous meningiomas, due to their rarity, are covered in few studies. They may present moderate to severe cerebral edema with a frequency of 74 to 88.9% due to hypervascularization, increased blood pressure, capillary permeability and secretion of VEGF (vascular endothelial growth factor). On magnetic resonance imaging, they may show more signs of flow voids, rarely present necrosis and tend to have homogeneous enhancement to paramagnetic contrast.

Meningiomas in pediatric patients present in atypical sites more frequently than in adults: lateral ventricles, skull base, posterior fossa. Intraventricular location occurs in 11%, compared to 0.3-3% in all ages and 0.5-4.5% in adults. Intraventricular meningiomas (IVM) are located in 76% of cases in the lateral ventricles (most common on the left side); 16% in the third ventricle; and 7% in the fourth ventricle. There are studies suggesting that the lateral ventricles are the preferred site for pediatric IVMs. These originate from the choroid plexus, growing in the tela choroidea. The vascularization of the tumor depends on its location in the ventricle: the nutrient vessels are of small caliber and usually originate from the choroidal arteries.

Clinically, pediatric IVMs are usually asymptomatic, until they reach large dimensions in the lateral ventricles, where the risk of hydrocephalus is lower. However, when located in the third or fourth ventricle, obstruction to the flow of cerebrospinal fluid can result in manifestations at early stages of tumor growth. Therefore, symptoms—headache, nausea, vomiting and visual disturbances—are more frequently related to tumor compression and an insidious increase in intracranial pressure. Indolent cognitive deficits compromising memory and attention may also occur. Typical symptoms of an acute increase in intracranial pressure are uncommon. The clinic, therefore, correlates with the location of the tumor within the ventricle, tumor size and the direction of its growth. Finally, we emphasize that the clinical presentation of the reported patient—convergent strabismus due to paresis of the right lateral rectus muscle—was not correlated with the tumor. This was still relatively small in size and its location did not justify the signs and symptoms.

IVMs usually have the classic radiological appearance of other meningiomas, well-defined globular shape, however no dural tail. They are usually iso to hypointense on T1-weighted images, hyperintense on T2-weighted images and suffer strong contrast enhancement. Especially in the pediatric population, other more frequent intraventricular tumors can make the differential diagnosis difficult: choroid plexus tumors, ependymoma, primitive neuroectodermal tumor, teratoma, and astrocytoma. Choroid plexus tumors usually affect younger than 10 years, and on MRI present a multilobulated mass with intense contrast enhancement and frond-like appearance. Ependymomas represent approximately one third of...
CNS tumors in children under 3 years of age and are characterized by necrosis, hemorrhage, cyst formation, and on MRI, they are hypointense on T1 and hyperintense and heterogeneous on T2.35

The surgical approach of a benign IVM is a neurosurgical challenge, given its deep location and its proximity to eloquent areas and vessels in the ventricular walls.5,34 The extent of the initial resection is an independent prognostic factor, presenting a significant association with recurrence and malignancy.2 The patient reported here did not present a recurrence in the 4 years of follow-up, which is a result consistent with the literature. In a 2012 review, with 201 cases from different series, there were only eight recurrences;27 however, in a meta-analysis with 677 cases of meningiomas in the first two decades, the numbers are more significant: there were 141 recurrences with an average presentation of 3.6 years and with mortality from this event in 46 cases.2 The recurrence in this age group occurs basically in cases of atypical meningiomas and anaplastic or after partial resection.36 Post-surgical mortality and morbidity in patients in the post-pubertal phase, as is the case of the patient reported here, are similarity to those observed in cases of meningioma in adults.2 The use of adjuvant radiotherapy should be avoided in young patients, opting for serial evaluation and reoperation in case of recurrence.2,3,8-11,14,18,37

In the literature, there are several surgical approaches for IVM resection: temporoparietal, transfrontal, middle posterior temporal gyrus, posterior inferior temporal gyrus, parieto-occipital and transcallosal.5,34 The choice is individualized and based on the location of the tumor within the ventricle, in tumor size and its vascular network, always with a objective of preserving the adjacent brain tissue, performing small corticectomy and retracting little as possible.5,6,27,30,33,34 The justification for the choice the approach is determined by the option that allows better access to the longest axis of the lesion, to minimize transcortical transgression, by the spectrum of preoperative neurological deficits, proximity to the eloquent structures, in addition to anatomical knowledge of the cortical and white matter.29 We chose the transcallosal approach because it allows better access to the frontal horn and lateral ventricle body. This approach prevents cortical damage; however, some care is needed with the possible presence of tributary cortical veins tributary of the superior sagittal sinus, which can be anticipated in preoperative examinations, and with the corpus callosum, which must be distinguished from the cingulate gyrus by the change in color.5 Despite the degree of difficulty, IVM surgery has shown low morbidity and mortality rates in recent decades, and most postoperative complications– visual deficits and praxis– are temporary.27,29,34 These low rates are consistent with the case reported here, which postoperative complications or sequelae did not occur.

IV. Conclusion

Intraventricular angiomatous meningioma is a rare entity, even more in patients in the first two decades of life. The clinic is nonspecific in most cases, making MRI evaluation necessary for the diagnosis and definition of the surgical approach, and the histopathological analysis is what defines the diagnosis of the angiomatous subgroup. Surgical resection is the treatment of choice. However, the goal of total resection should not be above the goal of preserving the patient’s functions and quality of life.
**Figure 1**: Preoperative MRI: A and B – T1 with gadolinium, axial (A) and coronal (B). Lesion with intense uptake at the level of the right frontal horn, close to the foramen of Monro. C and D – T2 axial(C) e coronal(D). Hyperintense lesion, with a focus of hypointense calcification (also seen in A).

**Figure 2**: A – Hematoxylin and eosin staining, 200 times magnification: image showing histopathological features of meningioma and significant vascular component. B – Immunohistochemistry, 400-fold magnification: tumor cells showing positivity for EMA.
Figure 3: Postoperative MRI: T1 with gadolinium, axial (A and B) and coronal (C and D) planes. Small residual focus near the foramen of Monro, attached to the thalamostriate vein (identified during the transoperative period).

Figure 4: Postoperative MRI: T2 axial (A and B) and coronal (C and D). Small residual focus at the level of the foramen of Monro (arrows).
RARE CASE OF YOUNG PATIENT WITH INTRAVENTRICULAR ANGIOMATOUS Meningioma

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Neuropathic Pain: Basic to Advanced Neuropathic Pain

By Santosh Nagare
Banaras Hindu University

Abstract- As we know that pain is the most common reason for which a patient takes medicine. Pain is not a single entity but may be classified as nociceptive pain, inflammatory pain, and neuropathic pain. Nociceptive pain such pain can be healed or cured by using NSAIDs and other analgesics. Neuropathic pain is caused by the direct lesion on the neuron or damage or dysfunction of peripheral or central neurons. Minor neuropathic can cured automatically because peripheral nervous systems neuron surrounded by Schwann cell which promotes the healing of neurons but CNS neurons don’t have Schwan cell they are covered with oligodendrocytes which don’t have self healing property so pain mediated through CNS are generally chronic. Even the smallest stimulation results in spontaneous intense pain after that it gets transformed into chronic pain syndrome which is difficult to treat.In chronic pain syndrome, plastic changes occur in nociceptive neurons which cant be reversed by pharmacological treatment. In this review, we have discussed the core pathophysiology of neuropathic pain and advances in it to date.

Keywords: neuropathic, NSAIDs, oligodendrocytes, chronic.

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I. Introduction

Steps in Neuronal Signal Processing: Sequence process occurs between pain initiation and the pain experience through ascending pathway[1].

1. Transduction: It’s the process by which a noxious signal gets transformed into an electrical signal so that it is carried towards the brain. In neuropathic, there is lesion or damage to the neurons so this mechanism is continuously on to produce the noxious signal. In the case of neuropathic pain when the nociceptor gets sensitized due to a signal it may recruit another silent receptor so that pain gets amplified this phenomenon is called Hyperalgesia. This afferent neuron sensitization is blocked by morphine by hyperpolarizing afferent neurons[2]. Neurons of this phase are termed as 1st order neurons.

2. Transmission: The phase ion which noxious stimulus is carried or transmitted towards the spinal cord then to the thalamus and cortex. For transmission there two main primary afferent nociceptive neurons which conduct signal according to stimuli with different speed.

C- Fibers
- Nonmyelinated
- Signal conducting range 0.5-2m/sec
- Sensitive to mechanical, thermal, chemical stimuli hence called C-polymodal nociceptors.

A-delta fibers
- Thin
- Myelinated
- Signal conducting range 2-20m/sec
- Generally, respond to only high threshold mechanical stimulation because to open such fibers strong stimulus is required to initiate and transmit the noxious signal. Because they require high potential to activate called High Threshold Mechanoreceptors.
- Some delta fibers respond to thermal stimuli also termed Mechano-thermal receptor.
- Neurons of this phase are termed second-order neurons and sensitization of these neurons called central sensitization leads to hyperalgesia and allodynia later.

Modulation: In this step, the noxious stimuli are modified intermediate neurons within the spinal cord and descending inhibitory system. Opioids act at the level of the spinal cord and inhibit dorsal horn neurons[3]. But beyond this morphine also produce its effect through periaqueductal central gray, medullary raphe, and spinal trigeminal nucleus too[4]. In the case of neuropathic pain descending inhibitory system is dysfunctional.

- Descending Modulatory system: This system activated at the level of periaqueductal (PAG) of the midbrain and these neurons then project downwards towards the medulla(nucleus reticularis gigantocellularis, nucleus raphe Magnus) and locus ceruleus which is the major source of NE[5]. The name of the pathway is descending inhibitory pathway itself indicates that it will inhibit the signal by promoting the release of neurotransmitters.
The distinct mechanism of Descending pain inhibitory pathways:

1. Descending neurons have direct contact with pain relay neurons of the spinal cord so electrical stimulation of the brainstem causes hyperpolarization of nociceptive receptors in the spinal cord and the release of neurotransmitters in descending pathway produces the inhibitory effect on ascending pathway so pain signal gets blocked at the spinal level.

2. The central terminal of the primary afferent neuron lies in the spinal cord and the central nociceptive receptor for neurotransmitter release in the spinal cord only by descending axon. To this postsynaptic response evoked by dorsal root at lamina 2 reduced by NE.

3. Superficial laminas of the spinal cord contain interneurons which contain inhibitory neurotransmitters like GABA, Glycine, Enkephalin. Descending pathway excites these interneurons of the spinal dorsal horn this will inhibit the ascending pain signal.

**Perception:** From second-order neurons, the signal is handover to the 3rd order neurons. Third-order neurons project to the somatosensory cortex and enable perception of pain through different parts[6], only Opioids able to inhibit pain perception no other drug able to do this.

### II. Pathophysiology of Neuropathic Pain

Diseases which causes spinal cord lesion are spinal cord injury, syringomyelia, multiple sclerosis, transverse myelitis, and neuromyelitis optica[7]. Peripheral neuropathies diabetes mellitus, HIV[8] and Leprosy, chemotherapy, immune and inflammatory disorder. Because of peripheral nerve lesion, there is an alteration in electrical properties of the sensory nerve which create the imbalance between the central excitatory and inhibitory system leads to complexity and chronic neuropathic pain.

**Peripheral Sensitization:** This means the sensitization is limited to the periphery only or the sensitization in which the brain and spinal cord are not involved.

Primary afferent neurons C-fibers and A-delta fibers are involved in peripheral sensitization these nociceptors respond best to the noxious stimuli. These pathophysiological changes are accompanied by cellular and molecular changes. The spontaneous activity of the injured nerve exactly matches with the expression of mRNA to increase the population of voltage-gated sodium channels. This increase in the population of voltage-gated sodium channels leads to the lowering of threshold potential. Now, this cluster of sodium channel not only accumulate at injured nerve but also to the proximity of dorsal root ganglia[9]. So that’s why pathophysiological changes in DRG are of particular therapeutic interest because DRG doesn’t have BBB so it’s easily accessible for systemic therapies[10]. Damage to peripheral nerve leads to upregulation of various receptor proteins which are expressed in very less quantity in normal physiology[11]. Ex. Vanilloid receptor (TRPV1), TRPV4. There are shreds of evidence that uninjured fibers also contribute to the pain signaling with injured fibers[12] Product Such as nerve growth factor are released in the vicinity of the nerve fibers that might trigger the release of TNF alpha and expression of the sodium channel, TRPV1, Adrenoreceptor thereby converts normal fibers into abnormal ones[13].

### III. Central Sensitization

Sensitization in the spinal cord— As a consequence of peripheral sensitization secondary changes occurs in the spinal cord dorsal horn. Peripheral neuronal damage leads to an increase in excitability of wide dynamic range neurons(WDRN). Wide dynamic range neurons are the neurons that respond to both painful and non-painful stimuli[14]. These neurons behave or work in graded response means as the strength of noxious stimulus increases results in increased pain sensation. This leads to hyperexcitability called central sensitization. This sensitization is maintained by pathological C-fibers by sensitizing the spinal cord dorsal horn to release glutamate act on postsynaptic NMDA receptor and neuropeptide substance P[15]. Central sensitization is maintained by an intracellular cascade of mitogen-activated protein kinase(MAPK)[16]. As soon as central sensitization is established then a small stimulus will responsible for the activation pain signal through low threshold A-beta and A-delta mechanoreceptor[17]. Central N-type of calcium channel located presynaptic membrane of primary afferent neuron plays important role in central sensitization by facilitating glutamate and substance P release[18].

**Advances in Neuropathic Pain Pathophysiology (Receptors and Mediators)**

- **Toll-like receptor 7**
  - Toll-like receptor 7 contributes to neuropathic pain by activating NF-κ B in primary sensory neurons. Toll-like receptors (TLRs) are a family of transmembrane pattern recognition receptors that mediate innate and adaptive immunity by recognizing exogenous ligands, pathogen-associated molecular patterns(PAMP), and danger-associated molecular patterns(DAMPs)[19]. TLRs not only expressed by the immune system but also neurons and nonneuronal cells express this receptor. To explore the potential role of DRG TLR7 in neuropathic pain, they examined whether TLR7 expression was altered in DRG and spinal cord following unilateral L4

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SNL, and results revealed that SNL, but not sham surgery, led to the time-dependent increases in expression of Tlr7 mRNA and its protein in the ipsilateral L4 (injured) DRG on days 3, 7, and 14 post-SNL. So they have further studied blocking of these TLR7 attenuates the pain hypersensitivity, so this overall result shows that DRG overexpression of TLR7 leads to neuropathic pain symptoms[20]. Increased expression of TLR7 increases the activation of NF-Kb in injured DRG leads to neuropathic pain symptoms.

- TLR8 in the Trigeminal Neuropathic Pain in Mice
  TLR8 is located in the intracellular endoplasmic reticulum (ER), endosomes, and lysosomes of DRG neurons, and plays an important role in the pathogenesis of spinal nerve injury-induced neuropathic pain[21]. TLR8 is mainly expressed in DRG and its expression is upregulated after SNL. Concluding pieces of evidence shown that TLR8 is necessary for maintaining neuropathic pain. This is achieved by delivering siRNA which will exclusively attenuate the TLR8 mediated pain state like mechanical allodynia and hyperalgesia. The results have been shown that TLR8 Expression is Increased in TG Neurons After pIONL-Induced TNP. Deletion of Tlr8 Reduces the pIONL-Induced Activation of ERK and p38, and the Expression of Pro-inflammatory Cytokines in the TG. Intra-TG Injection of TLR8 Agonist VTX-2337 Induces Pain Hypersensitivity. TLR8 Agonist VTX-2337 Increases the Ca^{2+} Concentration in TG Neurons[22].

- TLR signaling adaptor protein MyD88 in neuropathic pain
  The myeloid differentiation factor-88 adaptor protein (MyD88) mediates most TLRs (except for TLR3) signaling, as well as Toll/Interleukin receptor domain signaling through the interleukin (IL)-1 and IL-18 receptors. This protein in primary sensory neurons contributes to persistent inflammatory and neuropathic pain along with neuroinflammation. Studies have shown that selective deletion of Myd88 in Na_{1},8-expressing primary sensory neurons in CKO mice leads to reductions incomplete Freund's adjuvant (CFA) induced inflammatory and chronic constriction injury (CCI) induced neuropathic pain in the maintenance phase, without affecting basal pain and acute inflammatory pain[23].

- Sphingosine-1 phosphate receptor-1 in neuropathic pain
  S1PR1 Activation in astrocytes contributes to neuropathic pain. Based on genetic and pharmacological inhibition of S1PR1 with the different antagonists from different classes attenuated or even reversed neuropathic pain. S1PR1 Antagonist retains their capability to inhibit neuropathic pain without affecting endogenous circuity. However, this is limited to astrocyte-specific activation of S1PR1[24]. In addition to this administration of selective S1PR1 agonist SEW2871[25] caused the development of mechano-hypersensitivity in naïve mice[26]. S1P antagonism by FTY720/fingolimod results in a decreased chemotherapy-induced neuropathic pain[27]. Fingolimod also able to reduce the neuropathic pain in MS by inhibiting S1PR1 dependent central sensitization of the dorsal horn[28].

- P2X4 receptor in neuropathic pain
  A new concept of evoking neuropathic pain was proposed in which spinal microglia are activated after PNI(Peripheral Nerve Injury), and P2X4Rs on these activated microglia have an important role in evoking neuropathic pain[29]. P2X4 Receptor role in neuropathic pain is well established. The SNRIs duloxetine has an inhibitory effect on the function of microglial P2X4R so it's used in neuropathic pain treatment. Duloxetine inhibited microglial P2X4R function in addition to that Intrathecal administration of duloxetine attenuates mechanical allodynia after PNI(Peripheral Nerve Injury) that may be because of possible involvement ofP2X4R[30]. Upregulation of this ion gated receptor P2X4Rs is might be connected to fibronectin/integrin-dependent mechanism based on finding made on echistatin which blocks beta1 and beta3 integrins. In vitro studies have shown that echistatin down regulates the P2X4Rs upregulation[31]. P2X receptors are non-selective cation channels that open in response to ATP binding, allowing the rapid flow of ions (K+, Na+, Ca^{2+}) across the membrane but the calcium permeability is highest in the case of P2X4Rs, and stimulation of these receptors leads to the activation of p38 MAPK. This results in p38 MAPK activation and BDNF release as a key step in microglia-neuron communication leading to nerve injury-induced pain hypersensitivity[32]. This signaling further activates PLA2, liberating arachidonic acid (AA) and release of prostaglandin E2 (PGE2) that leads to hypersensitivity of peripheral pain pathways[33].

- PARP-1- Regulated TNF-Alpha expression in Neuropathic pain
  Poly-(ADP-Ribose) Polymerase 1 a Transcription regulator for TNF-Alpha. Its expression in DRG and SDH(Spinal Dorsal Horn) contributes to neuropathic pain pathogenesis in rats. This has the basis of lumbar 5 nerve ligation (L5 SNL) resulted in increased expression and activation of PARP-1 in DRG and the spinal dorsal horn[34]. PARP-1 Inhibitors impaired neuropathic pain states indicate their role in neuropathic pain. Studies have shown that PARP-1 involved in the regulation of inflammatory processes and functionally associated with transcription factor NF-Kappa B contributes to chronic inflammatory diseases[35].
• CCL2 (monocyte chemoattractant protein-1, MCP-1) in Neuropathic Pain

Activation of spinal microglia plays a critical role in neuropathic pain. Studies have shown that intrathecal CCL2 leads to spinal microglial activation and a neuropathic pain-like state. This acts as a precursor for understanding the further role of CCL2. Neutralizing Antibodies against CCL2 lead to inhibition of neuropathic pain behavior and microglial activation[36]. Thus CCL2 is involved in immune activation and maintaining sensitivity in neuropathic pain. Ryk (receptor-like tyrosine kinase) mediates excitatory synaptic transmission and also releases CCL2 in neuropathic pain and antagonism of RyK leads to decreased CCL2[37]. So because of this role modulation or inhibition of CCL2 responsible for attenuation of neuropathic pain. Minocycline is under study for neuropathic pain and its already been proven that it acts through down regulating microglial activation through CCL2 and CCR2[38].

• Melanocortin Type-4 Receptor in Neuropathic Pain

Melanocortin type-4 receptor is stimulated after nerve injury by α-MSH (Melanocortin Stimulating Hormone). This result in tonic pronociceptive response leads to sustaining the neuropathic pain. This idea leads to the development of a bifunctional compound which will act as an agonist on opioid receptor and antagonist of MC4 (Melanocortin 4 Receptor). Such compound produced effect at very low dose without affecting motor coordination in CCI mice[39]. It also investigated that MC4 Antagonism produced analgesia, anti-allodynic, anti-nociception and this observation further strengthen by Ligands VVK052 and VVK054 which show excellent affinity towards the human MC4 Receptor[40]. Tolerance in the case of opioid therapy is obvious the use of bifunctional ligand also shown the capability to decrease the tolerance[41]. These results showed the possibility of the melanocortin system and its receptor in neuropathic pain. Withdrawal symptoms and α-MSH induced hyperalgesia attenuated by the melanocortin-4 Receptor antagonist. The widespread distribution of melanocortin might be widely associated with neuropathic pain[42]. So prolonged blockade of melanocortin receptor (most probably MC4) results in alleviation or decreased of allodynia in rats with neuropathic pain[43].

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We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe InDesign, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

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Acknowledgments

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.
**Manuscript Style Instruction (Optional)**

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27” x 11””, left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word “Abstract” in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

**Structure and Format of Manuscript**

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper’s subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.
Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title
The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details
The full postal address of any related author(s) must be specified.

Abstract
The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords
A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods
Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations
Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations
Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends
Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.
Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Electronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.
6. **Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. **Revise what you wrote:** When you write anything, always read it, summarize it, and then finalize it.

8. **Make every effort:** Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. **Produce good diagrams of your own:** Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. **Use proper verb tense:** Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. **Pick a good study spot:** Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. **Know what you know:** Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. **Use good grammar:** Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. **Arrangement of information:** Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. **Never start at the last minute:** Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. **Multitasking in research is not good:** Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. **Never copy others' work:** Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. **Go to seminars:** Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. **Refresh your mind after intervals:** Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.
20. **Think technically:** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. **Adding unnecessary information:** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. **Report concluded results:** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. **Upon conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

**Informal Guidelines of Research Paper Writing**

**Key points to remember:**
- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

**Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

- **The introduction:** This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

- **The discussion section:**
  This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

- **General style:**
  Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

- **To make a paper clear:** Adhere to recommended page limits.
Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract:

This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.
The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study’s tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that’s all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer’s interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.
Results:
The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:
- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:
- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:
As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:
If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:
The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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