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OF MEDICAL RESEARCH: A

Neurology & Nervous System

Neurological Wilson Disease

Treatment of Psychiatric Disorders

Highlights

A Case of GM 1 Gangliosidosis

Untangling Psychology from Biology

Discovering Thoughts, Inventing Future

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Untangling Psychology from Biology in the Treatment of Psychiatric Disorders

By Michael Raymond Binder, M.D.

Abstract- Due to the lack of a clear distinction between mentally-driven psychiatric symptoms and neurologically-driven psychiatric symptoms, determining which patients would best be treated with psychotherapy, which patients would best be treated with pharmacotherapy, and which patients would best be treated with both is a challenge that every behavioral health clinician faces. In an effort to overcome this challenge, this article will discuss the anatomical and functional relationship between the mind and the brain as it relates to the various treatment options that are currently available and introduce a groundbreaking new paradigm that is destined to transform the treatment of mental illness from a symptom-based practice to a pathology-based practice.

Keywords: *psychotherapy, medication, biomarkers, mind-brain dynamics, neuronal hyperexcitability, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, treatment options.*

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Untangling Psychology from Biology in the Treatment of Psychiatric Disorders

Michael Raymond Binder, M.D.

Abstract- Due to the lack of a clear distinction between mentally-driven psychiatric symptoms and neurologically-driven psychiatric symptoms, determining which patients would best be treated with psychotherapy, which patients would best be treated with pharmacotherapy, and which patients would best be treated with both is a challenge that every behavioral health clinician faces. In an effort to overcome this challenge, this article will discuss the anatomical and functional relationship between the mind and the brain as it relates to the various treatment options that are currently available and introduce a groundbreaking new paradigm that is destined to transform the treatment of mental illness from a symptom-based practice to a pathology-based practice. In addition to putting the assessment and treatment of mental illness on par with other medication specialties, the new paradigm ushers in the first objective way to distinguish biologically-based psychiatric symptoms from psychologically-based psychiatric symptoms. This is of critical importance because it has the potential streamline treatment, better define the target for treatment, and more accurately inform the planning of treatment. It also has the potential to improve patient education and treatment outcomes by better explaining how psychotherapy works, how pharmacotherapy works, and how these two treatment modalities can complement or, in some cases, antagonize each other. Beyond all of these advantages, the new paradigm offers the potential to ward off psychiatric symptoms before they even begin. With the prevalence of psychiatric and substance use disorders at epidemic proportions, these long-awaited advances could not be more timely.

Keywords: *psychotherapy, medication, biomarkers, mind-brain dynamics, neuronal hyperexcitability, antidepressants, antipsychotics, psychostimulants, anticonvulsants, mood stabilizers, neuroregulators, mental health, treatment options.*

I. INTRODUCTION

Both in the United States and other developed countries, the prevalence of anxiety, depression, and other common psychiatric disorders has reached epidemic proportions. Consequently, there is a desperate need for improved treatment outcomes, yet the effectiveness of mental healthcare is not much better now than it was fifty years ago [1]. Psychotherapists continue to employ various psychotherapeutic techniques, and psychiatrists continue to prescribe antidepressants, antipsychotics, and psychostimulants in various combinations. Typically, patients who have

relatively mild psychiatric symptoms enter the behavioral healthcare system by consulting with a psychotherapist in the hope of avoiding treatment with medication. Patients who have more severe symptoms sometimes initiate treatment with a psychotherapist, sometimes with a psychiatrist, and sometimes with both. There are also some patients who initiate treatment with an internist and then either continue with the internist or receive a referral to a specialist. Unlike in the past, most contemporary psychiatrists do not practice psychotherapy, and most psychotherapists exhaust the benefits of their craft before referring the patient to a psychiatrist. One of the fundamental problems with this triage system is that patients largely self-select the modality of treatment they receive. Another problem is that there is no objective way to determine which patients would best be treated with psychotherapy, which would best be treated with medication, and which would best be treated with a combination of the two. Yet another problem is the potential lack of communication between the psychotherapist and the psychiatrist when both services are being provided simultaneously. These potential problems underscore the need for clinicians and prospective patients to better understand the mechanisms through which various psychotherapeutic and psychopharmacologic treatment modalities exert their therapeutic effects and to be able to determine, more objectively, which treatment modality would be most appropriate for which patient.

In this article, current psychological and biological approaches to treatment will be reviewed, and a new formulation of the dynamic interplay between the mind and the brain will be discussed. From this fresh perspective, the puzzling relationship between mental processes and neurological processes will be clarified, and a new way of conceptualizing mental illness will be proposed. Based on this new conceptualization, which is strongly supported by converging lines of evidence, the first objective method of determining which patients should be treated with which modality—psychotherapy or biological therapy—will be introduced and, by offering the potential to treat mental illness based on pathology rather than symptomatology, a new era of behavioral healthcare will be ushered in.

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II. CURRENT APPROACHES TO MENTAL ILLNESS AND HOW THEY WORK

a) *Psychological Interventions*

i. *Supportive Psychotherapy*

Considered to be at the heart of all clinician-patient relationships, supportive psychotherapy encourages the patient to express his or her thoughts, feelings, and concerns in a safe, confidential, and nonjudgmental environment. Though helpful in treating almost any clinical condition, the precise mechanism (or mechanisms) through which supportive psychotherapy exerts its therapeutic effects are still not fully understood. However, its primary therapeutic mechanism appears to be stress-reduction.

ii. *Psychoanalytic Psychotherapy*

As the dominant form of therapy during the late 19th to mid20th centuries, psychoanalysis is aimed at helping patients resolve unconscious psychological conflicts by allowing them to become more aware of their unconscious thoughts, drives, and motives. The pioneer of this technique, Sigmund Freud, believed that as patients progressed, they became less stressed, less defensive, and, thus, less neurotic. However, the neurological correlates of these changes and their relationship to the patient's symptoms are still unclear.

iii. *Interpersonal Psychotherapy (IPT)*

IPT focuses on relieving psychiatric symptoms by improving interpersonal functioning and social support. The central tenant of IPT is that psychiatric symptoms are the consequence of current difficulties in one's relationships with others. Hence, the belief is that symptoms can be reduced by addressing current social stressors and helping patients develop healthier ways of relating to others. However, as with psychoanalytic psychotherapy, the effects of these changes on neurological function are still unclear.

iv. *Existential Psychotherapy*

Developed out of the philosophies of Friedrich Nietzsche and Søren Kierkegaard, existential psychotherapy hypothesizes that stress, frustration, and human discontent can be overcome through wisdom, willpower, and accepting personal responsibility. As a patient's stress levels decline, so too will his or her psychiatric symptoms. However, the neurological mechanism through which the patient's symptoms decline is still unknown.

v. *Cognitive-behavioral Therapy (CBT)*

CBT, which is commonly used for a wide range of mental health conditions, focuses on how one's thoughts, beliefs, and attitudes affect their feelings and actions. By replacing one's negative, self-defeating, and self-destructive thoughts with positive, self-affirming, and productive thoughts, one can reduce their psychiatric symptoms and literally change the way their

brain processes information [2, 3]. However, the theory behind CBT does not answer the question of why some persons develop negative ways of thinking whereas others do not despite being raised in the same household by the same parents. It also fails to explain how the neurological changes that occur in conjunction with the observed cognitive and behavioral changes translate into a reduction of psychiatric symptoms.

vi. *Dialectic-behavioral Therapy (DBT)*

Based on the principles of CBT, DBT is specifically designed to help persons who experience their emotions too intensely. The DBT therapist helps the patient to combine opposing or "dialectic" cognitions and emotions to achieve a more positive way of thinking and feeling about things. In so doing, one's stress levels and, thus, one's psychiatric symptoms are reduced. However, DBT does not explain why, either psychologically or neuropsychiatrically, some persons experience their emotions more intensely.

vii. *Biofeedback*

Biofeedback attempts to reduce mental, emotional, and physical symptoms by teaching a person to control various functions of his or her body, such as heart rate, respiratory rate, and muscle tone. In theory, the meditative aspect of this discipline combines with a sense of empowerment over physical symptoms to reduce cognitive-emotional distress. Thus, biofeedback has the potential to reduce psychiatric symptoms as well as their associated physical symptoms. However, this treatment approach neither hypothesizes nor addresses the underlying cause of the symptoms.

viii. *Eye Movement Desensitization and Reprocessing (EMDR)*

Initially intended to help reduce symptoms of post-traumatic stress disorder, EMDR attempts to facilitate cognitive-emotional healing by alternately activating, with either voluntary eye movements or physical stimuli, the left and right sides of the body and then asking the patient to capture and hold in his or her mind, while the alternating stimulus is repeated, whichever thoughts and emotions were experienced. Although the mechanism by which EMDR exerts its therapeutic effects is not fully understood, the technique is thought to activate some of the same neurological recovery processes that occur during rapid eye movement (REM) sleep.

ix. *Mindfulness Meditation*

In mindfulness meditation, patients are asked to step back and reflect on the way they are thinking and feeling about individual emotional stressors and before they respond to them. This allows them to gain insight into their attitudes and behaviors and to develop a higher degree of self-discipline and self-control. Included in the technique are breathing exercises, guided imagery, and other practices that help relax the

mind and body. Through this relaxation processes, psychiatric symptoms are reduced and one's self-confidence is increased. However, the neurological mechanism through which this healing takes place remains unclear.

b) *Medical Interventions*

i. *Psychotropic Medications*

a. *Antidepressants*

Antidepressants are the mainstay of treatment for anxiety, depression, and a number of related psychiatric disorders. The serendipitous discovery of the antidepressant effect back in the 1950s led to the monoamine hypothesis of depression, which posited that a deficiency of monoamines was the core abnormality in clinical depression [4]. Although this could not explain why the antihypertensive drug reserpine, which lowers the activity of monoamines, was likewise effective in reducing symptoms of depression [5], the monoamine hypothesis has guided the use of antidepressants for more than fifty years. More recently, however, several other weaknesses of the monoamine hypothesis have been identified. Chief among these are its failure to explain how antidepressants can be effective in treating psychiatric disorders other than clinical depression [4]; why a depletion of serotonin precursors does not produce symptoms of depression in healthy subjects [6]; and why antidepressants can sometimes cause a paradoxical worsening or cycling of symptoms [7-10]. It also fails to explain how the purported abnormalities in monoamine transmission actually translate into depressive symptomatology [11].

b. *Antipsychotics*

Also known as "major tranquilizers," antipsychotic drugs were originally used to treat agitation, hallucinations, and delusions in schizophrenia. However, they are increasingly being used to augment the effects of antidepressants and mood stabilizers in the treatment of clinical depression and bipolar disorder. Pharmacologically, antipsychotic drugs exert a host of neuroinhibitory effects, including blockade of histamine, dopamine, norepinephrine, and acetylcholine receptors [12], and although dopamine is known to play an important role in auditory signaling [13], the precise mechanism by which antipsychotic drugs exert their wide-ranging therapeutic effects has heretofore remained unclear.

c. *Psychostimulants*

Although these drugs were initially used to treat ADHD, they are now being used to treat a variety of co-occurring symptoms, such as anxiety, depression, apathy, and drowsiness. Psychostimulants are thought to exert their therapeutic effects by increasing catecholaminergic transmission in the brain. However, as with antidepressants and antipsychotics, the precise mechanism by which their pharmacological effects

translate into their cognitive-emotional effects remains unclear.

d. *Anticonvulsants*

More commonly known in psychiatry as "mood stabilizers," the use of anticonvulsants is largely reserved for bipolar spectrum disorders because of their ability to stabilize mood. Although the precise mechanism by which they exert this clinical effect has heretofore remained unclear, anticonvulsants are known to reduce neuronal excitability by a number of mechanisms, including augmentation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [14], potentiation of GABA receptor activation [15], and reduction of sodium and calcium flux across neuronal membranes [16, 17].

e. *Ketamine*

In recent years, ultra-low doses of the dissociative anesthetic ketamine have been found to exert some of the most rapid and robust antidepressant effects yet to be observed [18]. Unfortunately, however, ketamine is relatively short-acting, has a narrow therapeutic index, and can be cumbersome to administer [19]. With repeated dosing, it also carries the risk of cognitive impairment, tolerance, and withdrawal [19]. However, the rapid and robust therapeutic effects of ketamine have drawn intense interest to its pharmacological effects. The drug is known to be an antagonist of the excitatory neurotransmitter glutamate, thus implicating glutamate in the pathophysiology of depression and possibly other psychiatric disorders.

f. *Neuroactive Steroids*

Recognizing that the postpartum period is a time of both increased vulnerability to depression and sharp fall in serum progesterone levels, derivatives of progesterone are now being investigated for use in treating clinical depression and bipolar disorder [20-22]. Although preliminary data look promising, a potential limitation of these drugs is a loss of therapeutic effect over time. This concern is based on previous experience with other positive allosteric modulators of the GABA-A receptor, such as barbiturates, benzodiazepines, and sedative hypnotics, all of which carry the risk of tolerance, dependence, and withdrawal. However, the therapeutic success of GABA-A receptor modulators, which put a break on neuronal firing, reiterates the importance of calming the brain in the treatment of psychiatric disorders.

ii. *Somatic Therapies*

a. *Electroconvulsive Therapy (ECT)*

Still regarded as the gold-standard in the treatment of clinical depression, ECT involves the intentional induction of seizure activity in the brain. Although the mechanism by which ECT exerts its therapeutic effects remains unclear, it is evident that clinical improvement occurs not during the seizure but in

the aftermath of the seizure. It is now recognized that seizures are brought to a halt by a host of neuroinhibitory changes that occur in response to the seizures themselves. Known inhibitory mechanisms include glutamate depletion, GABAergic recurrent inhibition, membrane shunting, depletion of energy stores, loss of ionic gradients, endogenous neuromodulator effects, and regulatory input from various brain regions [23]. Hypothetically, this cascade of neuroinhibitory responses explains why ECT is an effective treatment for status epilepticus [24, 25]. Also, based on the known psychotherapeutic effects of calming the brain, the need for a cumulative effect could explain why a course of several ECT treatments is typically needed to achieve a substantial and lasting reduction of psychiatric symptoms. Since its introduction in the late 1930s, the use of ECT has expanded to bipolar disorder, delusional disorder, obsessive-compulsive disorder, schizophrenia, schizoaffective disorder, catatonic states, and neuroleptic malignant syndrome [26], thus reiterating the wide-ranging therapeutic effects of calming the brain and suggesting that many psychiatric disorders could have a shared pathophysiology.

b. *Repetitive Transcranial Stimulation (rTMS)*

As one of the newest techniques for treatment-resistant depression, rTMS uses electromagnetic induction to non-invasively depolarize or hyperpolarize neurons in the brain. Consistent with the idea that specific neurological processes affect the corresponding cognitive-emotional processes, rTMS is thought to exert its therapeutic effects by modulating the activity of specific neuronal circuits [27].

c. *Deep Brain Stimulation (DBS)*

Also known as “brain pacemaker,” DBS involves the selective stimulation of specific brain areas via an implanted electronic device. The technique is thought to exert its therapeutic effects by correcting the firing imbalances of neuronal circuits that are believed to be associated with the patient’s symptoms. Thus, for example, in severe intractable depression, symptoms are thought to be relieved by stimulating brain areas that would normally be more active in non-depressed persons. This mimics the effects of psychotropic drugs and rTMS in that it modulates neuronal signaling.

d. *Vagus Nerve Stimulation (VNS)*

VNS is another “pacemaker” technique that involves the surgical implantation of electrodes (in this case into the chest) to stimulate specific circuits in the brain. It is used in the treatment of seizure disorders, mood disorders, and chronic pain that is resistant to pharmacotherapy. After the VNS device is inserted under the skin, a wire is connected to the vagus nerve in the neck. Through this connection, the neurostimulator delivers thirty-second pulses of electricity to the vagus nerve, which feeds into the solitary tract nucleus.

Afferents of the solitary tract increase the activity of the inhibitory neurotransmitter GABA while at the same time reducing the activity of the excitatory neurotransmitter glutamate. Solitary tract afferents also promote norepinephrine signaling via projections to the locus coeruleus and amygdala [28]. This combination of effects is thought to explain the therapeutic effects of VNS in treatment-resistant depression.

e. *Stellate Ganglion Block (SGB)*

SGB is now being used to treat a number of conditions, including complex regional pain syndrome, high blood pressure, and some psychiatric disorders, particularly post-traumatic stress disorder [29]. The stellate ganglion is present in approximately 80% of the general population and is composed of the inferior cervical ganglion and the first thoracic ganglion fusion. It is located posteriorly in the neck at the level of the seventh cervical vertebra. SGB involves anesthetizing the stellate ganglion so as to reduce the sympathetic outflow that is relayed through it. In so-doing, the ratio of sympathetic-to-parasympathetic output is reduced, thus helping to quell the flight-or-flight response. As with nearly all of the aforementioned medical interventions, symptom reduction occurs in association with calming the nervous system, thus reiterating the therapeutic value of neuroinhibition in the treatment of psychiatric symptoms.

III. A NEW WAY OF CONCEPTUALIZING MENTAL ILLNESS

a) *Anatomical and Functional Relationship Between the Mind and the Brain*

With the birth of neuroscience, the historical idea that the soul was the seat of thoughts and emotions was replaced with the reductionist idea that thoughts and emotions were the products of complex brain function. However, a burgeoning number of eyewitness reports and testimonials from around the world is beginning to reawaken the idea that consciousness is possible both in conjunction with and independent of brain function. There are now millions of people from diverse ethnic, cultural, and religious backgrounds who claim to have had vivid out-of-body experiences during a close brush with death or, in some cases, an actual pronouncement of death [30-35]. During these so-called near-death experiences (NDEs), those who have had them claim to have left their physical bodies and continued to think, perceive, and remember things that, based on the reductionist view, would have been physically impossible [30-35]. Moreover, many of these accounts have been corroborated by factual information that the NDErs could not possibly have known had they not actually separated from their physical bodies and retained their cognitive, sensory, and memory functions [30-35]. The evidence is now so strong that, in 2022, the New York Academy of Sciences published a

multidisciplinary consensus statement concluding that “NDEs are not hallucinations or illusions but rather evidence that life continues after death” [36].

According to NDErs, the mind, when separated from the body, is even more lucid, more aware, and more knowledgeable than when it dwells in the body. This suggests that the brain, rather than being the extraordinary information processor that it has been touted to be, is actually slowing down and limiting mental function. However, what NDErs also report is that they were unable to interact with the physical world while outside their physical bodies. Thus, the brain appears to be acting as a biological transducer that translates mental signals into neurological signals. The reverse process also appears to occur: the brain appears to stimulate specific thoughts and emotions in the mind, thus creating a two-way dialogue between the mind and the brain.

That this mind-brain dialogue actually occurs has now been demonstrated experimentally. Recording from single neurons in patients implanted with intracranial electrodes for clinical reasons, Cerf et al. [37] found that willful thoughts and emotions readily stimulated specific neurons when subjects were asked to perform specific mental tasks. Conversely, stimulating different parts of the brain with an electrical probe has long-been known to trigger different thoughts and emotions [38]. However, this mind-brain dialogue gives rise to the historic mind-body problem: how can the mind and the body communicate with each other if their natures are different? The answer to that question may be supplied by modern advances in biology, chemistry, and physics.

Like all forms of energy, mental energy would be expected to induce magnetic fields. Likewise, the neurons of the brain induce magnetic fields as they depolarize and repolarize. Hence, the mind and the brain are naturally poised to communicate in the same language—electromagnetic energy. Besides helping to explain both the emerging data on NDEs and the experimental observations of Cerf and his colleagues, a duality of mind and brain could, for the first time, explain the distinction between unconscious and conscious mental processing. Unconscious mental processing would occur independent of brain function, whereas conscious mental processing would occur when neurologically-induced magnetic fields synchronized with mentally-induced magnetic fields (Figure 1). This synchronization process hypothetically explains the familiar time-delay when the mind attempts to formulate a thought or draw a memory into consciousness. Consciousness, in this sense, could more aptly be called “corporeal consciousness” because it occurs in conjunction with neurological function. This is in contrast to “incorporeal consciousness,” which would occur independent of neurological function [11]. Note also that unconscious mental processing, being electromagnetic

but independent of neurological function, would proceed at a speed of approximately 300,000,000 meters/second (the speed of electromagnetic waves). This is in contrast to conscious mental processing, which, being dependent upon neurological function, would proceed at the relatively slow speed of about 150 meters/second (the speed of salutatory conduction) [39]. This difference, together with the uncoupling of the mind from bodily sensory systems during an NDE, could explain why NDEers experience such a dramatic expansion of consciousness when they separate from their physical bodies [31-34].

Further evidence that the mind is capable of functioning independent of the brain comes from the observation that children who are born without a cerebral cortex are conscious [40], and in their pioneering work, Wilder Penfield and others found that awareness of self and environment were fully preserved as they surgically removed relatively large areas of the cortex to treat refractory seizures [40, 41].

That leads to the question of where in the body the mind is located. Based on the observation that injury to anybody-part other than the head leaves corporeal consciousness intact, it is evident that the mind is located in the head. Also, with the exception of damage to the neurological system, damage to any part of the body can be perceived by the mind. That implies that the mind-body connection must be dependent upon intact neurological function. The only part of the neurological system that is in the head is the brain. Therefore, the mind-body connection must occur in the brain.

Although it would be difficult to pinpoint where in the brain the mind is located, the topography and functional anatomy of the brain provide important clues. It is well-recognized that virtually all sensory input is relayed directly to the thalamus. It is also known that the thalamus remains a part of the conversation as the input is being processed by the cerebral cortex and other parts of the brain [42]. Furthermore, even mild damage to the thalamus can result in a vegetative state [43]. Conversely, deep brain stimulation of the thalamus has been found to be of some benefit in rousing patients from a minimally conscious state [44, 45]. Hence, it appears that the thalamus, which has been called “the gateway to the mind,” could be acting as a functional interface that allows the mind to monitor and control virtually every function of the brain and body [11]. That would place the mind, or at least its primary area of focus, at the core of the brain.

Mind-Brain Interactions



Figure 1: Schematic illustration of the mind (large white burst) communicating with the brain via the synchronization of mentally-induced magnetic fields (white radiations) and neurologically-induced magnetic fields (red radiations).

b) Practical Application of Mind-Brain Dynamics to the Diagnosis and Treatment of Mental Illness

The idea that the mind and the brain are two distinctly different entities that interact with each other could begin to explain how treatment with psychotherapy alone and medication alone can achieve similar results both psychologically and neurologically [46]. Therapies that are aimed directly at changing the way one thinks would have secondary affects on the brain because everything that is processed by the mind would simultaneously be processed by the brain. Conversely, therapies that are aimed directly at modulating brain function would have secondary effects on the mind because everything that is processed by the brain would simultaneously be processed by the mind. Thus, for example, cognitive-behavioral therapy, which changes the way one thinks and feels, would retrain circuits in the brain because changes in cognitive-emotional processing alter neuronal firing patterns. Conversely, pharmacological therapy, which modulates the activity of specific neuronal circuits, would retrain one's thoughts and emotions because changes in neuronal signaling cause changes in mental and emotional processing.

The big question when it comes to therapy, however, is which form would be most effective for which patient? To answer that question, one would first need to determine which of the two—the mind or the brain—was the primary driver of the symptoms. One would then need to determine which form of therapy, when used to treat the appropriate part of the cognitive-emotional system, would be best for which patient. However, the answer to both of these questions would

depend upon an accurate understanding of what causes psychiatric symptoms to begin with.

Although the precise cause of psychiatric symptoms remains unclear, an emerging hypothesis contends that psychiatric symptoms are driven by pathological hyperactivity in symptom-related circuits in the brain. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, pathological hyperactivity in anxiety circuits causes elevated and persistent feelings of anxiety; pathological hyperactivity in depressive circuits causes elevated and persistent feelings of depression; and pathological hyperactivity in cognitive circuits causes racing thoughts and obsessional thinking [47]. Yet, that would still fall short of explaining why the symptom-related circuits in the brain become pathologically hyperactive.

However, a possible answer to that question is supplied by the gene research. A number of large, multi-center gene association studies have found that persons who suffer from common psychiatric disorders, such as anxiety, depression, bipolar disorder, and schizophrenia, have gene variants whose protein products fail to adequately regulate the firing of neurons [48-61]. Now then, given that all of the most common psychiatric disorders are essentially different combinations of the same symptoms, it would not be unreasonable to think that all of these disorders could be rooted in a shared physiological abnormality; namely, neuronal hyperexcitability. Hyperexcitable neurons would just fire too easily and fail to shut off when they should. Indeed, this aligns with the neurophysiological abnormalities that have been

observed on functional [62] and electroencephalographic [63] studies of depression.

Now imagine that an affected person were confronted with a stressful situation. The hyperexcitability of the neurons would cause all of the person's anxious thoughts to run through his or her mind more times than they should, and it would cause all of the person's uneasy emotions to be abnormally intense and persistent. In addition to being experienced as inappropriately excessive worry and anxiety, the added mental and emotional tension would cause the related circuits in the brain to be further stimulated, thus creating a vicious cycle of mutual overstimulation between the mind and the brain. Moreover, this vicious cycle would, over time, be further amplified by "primed burst potentiation," a natural kindling effect through which neurons that are repeatedly stimulated become increasingly responsive to further stimulation [64].

Another factor that would add fuel to the fire is the tendency for neuronal circuits to compete for dominance. From the study of epilepsy, it is known that pathologically hyperactive circuits tend to inhibit the activity of competing circuits [65]. This phenomenon would tend to prevent the mind from shifting attention to less anxious and more productive thoughts. In other words, it would leave the mind and the brain caught in the "default mode," a psychophysiological state of unproductive internal processing that has been observed on functional imaging of clinical depression and other neuropsychiatric disorders [66]. It could also lead to aberrant circuit induction. This process, which is analogous to a short-circuit in a wired electrical system, hypothetically involves the inappropriate stimulation of relatively hypoactive circuits by pathologically hyperactive circuits [67]. As the feeder circuits quiet down due to synaptic fatigue [68], the freshly activated receiver circuits cause the person's thoughts and emotions to shift accordingly, thus driving the "bipolar switch" [67]. With all of this abnormal electrical activity hijacking the cognitive-emotional system, it is not surprising that affected persons are so easily overwhelmed, so emotionally unstable, and so plagued with self-doubt.

This raises the question of what really drives patients to seek treatment. The natural assumption is that they are driven to seek treatment by the factors that they say drove them to seek treatment. However, as one can see from the forgoing discussion, those factors can be abnormally amplified and distorted by poorly restrained discharges from the brain. Yet in actual practice, neither patients nor their healthcare providers have any reliable way of knowing this. In the 1900s, mild cognitive-emotional distortions were referred to as "neuroses," and severe cognitive-emotional distortions are still referred to as "psychoses." According to the MCNH hypothesis, various forms of psychosis are created when, due to the amplifying effect of neuronal

hyperexcitability, the intensity of mentally-generated thoughts and emotions becomes as high or higher than the intensity of thoughts and emotions that would normally be driven by input from the eyes, ears, and other sensory organs. Hypothetically, the margin between internally-driven thoughts and emotions, which are normally of lower intensity, and externally-driven thoughts and emotions, which are normally of higher intensity, is what allows a person to distinguish internal from external reality. Of course, the distorting effect of neuronal hyperexcitability can easily be recognized in severely psychotic patients; but the distorting effect can be more difficult to recognize in patients whose complaints are less out-of-line with reality. If the therapist then begins to work with this distorted content in such patients, he or she would unwittingly be attempting to treat a neurological problem with a psychological intervention. By analogy, it would be like trying to correct impaired vision by talking about it. The difference, however, is that talking about a visual impairment cannot do further damage to the eye; whereas, talking about neurologically-distorted thoughts and emotions can cause further damage by continuing to stir the pot, particularly in a person whose hyperexcitable brain is continuing to distort everything that he or she thinks and feels. Most experienced psychotherapists can readily attest to the risk of regression when intensive psychotherapy is attempted with more severely disturbed patients (presumably those with higher levels of neuronal hyperexcitability), and the renowned Austrian psychiatrist Sigmund Freud, due to the same concerns, was careful to avoid psychoanalyzing psychotic-range patients [69].

In contrast to persons with hyperexcitable brains, those with normoexcitable brains would be relatively resistant to cognitive-emotional stress, and they would be even more resistant to developing psychiatric symptoms. That raises the possibility that most, if not all, persons who present for psychotherapy have hyperexcitable brains. Additional support for this idea comes from the observation that the vast majority of persons who initially seek the care of a psychotherapist rarely need to continue psychotherapy once, upon being referred to a prescriber, their neurological function is normalized with anticonvulsant drugs. Another observation that suggests that most persons who seek psychotherapy have hyperexcitable brains is that such persons are rarely satisfied with their treatment until they either become willing to accept medical therapy or they establish natural brain-calming habits and routines, such as stress-reduction, establishment of an early sleep schedule, regular exercise, avoidance of psychostimulants, and minimization of refined sugar. Consistent with this observation, the Royal Australian and New Zealand College of Psychiatrists is now, for the first time, recommending attention to diet, regular exercise, and

sleep hygiene as “non-negotiable first steps” in the treatment of major depressive disorder [70].

Another important factor to consider is that the majority of studies that compare the effectiveness of psychotherapy alone to pharmacotherapy alone involve the use of antidepressants, and antidepressants are not the appropriate treatment for neuronal hyperexcitability [67, 71, 72]. Still, such studies yield comparable results [73], an observation that calls psychotherapy into question as much as the use of antidepressants. That is not to say that psychotherapy, as a therapeutic tool, is unhelpful, but only to say that most persons who seek psychotherapy would be better served if they were to simultaneously be assessed for neuronal hyperexcitability. If this common condition could be identified and treated successfully early in the course of psychotherapy, the distorting element of the patient's distress would be minimized, and the therapy could focus more on matters that truly were rooted in psychology, such as attitude, values, and priorities. Some of the aforementioned psychotherapeutic techniques do just that, whereas others analyze the patient's distressing thoughts and emotions.

What all of the psychotherapeutic techniques have in common, however, is that they aim to reduce intrapsychic tension. Reducing intrapsychic tension has both direct and indirect benefits; it benefits the mind directly by bringing psychological relief, and it benefits the brain indirectly by reducing mental stimulation of the brain. However, as previously discussed, intrapsychic tension can be difficult to reduce when the pathologically hyperactive brain is keeping the mind bathed in stress. That underscores the importance of pharmacotherapy. If the brain could be quieted directly through anticonvulsant drugs (or any of the aforementioned medical therapies), the interference from the brain would be reduced, thus explaining why medical therapy tends to work faster than psychotherapy [46] but not as well as when combined with psychotherapy [74].

Notwithstanding the potential benefits of medical therapy, it should be noted that antidepressants, psychostimulants, and some of the other medical therapies that were referenced earlier stimulate some parts of the brain while calming others. For example, SSRIs increase neuronal firing in the cerebral cortex [75] but reduce neuronal firing in the amygdala [76], and rTMS can be used to either stimulate or inhibit the activity of specific neuronal circuits [77, 78]. Although increasing the activity of specific circuits can be therapeutic, it can also be counter-therapeutic, depending on how it affects the circuit-specific imbalances that are driving the patient's symptoms. This is the MCNH explanation for the paradoxical effects that neuroactivating medical therapies, particularly antidepressant and psychostimulant therapies, can have. With these two

classes of drugs topping the list of the most commonly prescribed medications, and the prevalence of psychiatric and substance use disorders at epidemic proportions, the need to better understand how these drugs and other medical therapies are affecting the mind and brain is evident.

IV. ASSESSING THE RELATIVE IMPORTANCE OF THE NEURONAL HYPEREXCITABILITY TRAIT

But even if neuronal hyperexcitability were at the root of psychiatric symptoms, it would not discount the importance of numerous other factors, such as family upbringing, childhood trauma, ongoing stressors, and personal choices. However, an analysis of the family pedigrees of persons who exhibit signs of mental illness is quite revealing. Although family, twin, and adoption studies have historically failed to identify a classic Mendelian pattern of inheritance for any of the common psychiatric disorders, a reconceptualization of psychiatric symptoms as the symptomatic expression of the neuronal hyperexcitability trait does reveal a classic Mendelian distribution. That distribution is strikingly autosomal dominant! [47]. In other words, in those families that are affected, probands who develop either subsyndromal or more obvious signs and symptoms of mental illness, such as a diagnosable psychiatric, functional physical, or substance use disorder, almost always appear in a classic autosomal dominant distribution. Moreover, a predictable subset of children in these families are completely unaffected despite being raised in the same households by the same parents. These so-called “survivors,” who typically appear in an autosomal recessive distribution, are presumably those who did not inherit one of the gene variants that have been linked to neuronal hyperexcitability. These observations combine to suggest that: 1) all of the most common psychiatric and functional physical disorders are rooted in the same biological abnormality; 2) all of these disorders may be driven by polymorphisms of a single gene locus; and 3) the hypothesized abnormality may be the most important predisposing factor in the development of these disorders. While recognizing their profound importance, these observations should be interpreted with caution because they are based on informally-obtained family pedigrees (approximately 300) rather than tightly controlled studies [67, 79].

V. THE CHALLENGE OF IDENTIFYING THE NEURONAL HYPEREXCITABILITY TRAIT

Although the phenomenon of neuronal hyperexcitability as a possible driver of psychiatric symptoms has been described previously [47, 80], its significance has been sorely overlooked. This is largely due to the elusive nature of the neuronal hyperexcitability trait. The reasons for the difficulty

identifying the trait are complex and multi-faceted. Some, but not all, will be discussed here for the purpose of illustration.

The most fundamental reason that the neuronal hyperexcitability trait has been so difficult to identify is that the trait has heretofore been undetectable by any form of laboratory testing, neuroimaging, or electroencephalography. Hyperexcitable neurons, like a hive of irritable bees, cannot be distinguished from normoexcitable neurons until the metaphorical bees are disturbed. However, even then, the brain does not become hyperactive as a whole. Rather, the pathological hyperactivity occurs in the brain's microcircuitry [81], where it can easily be overlooked or considered to be normal on diagnostic studies. The same challenge is experienced clinically, as carriers of the trait can be completely asymptomatic until something or someone begins to stress them. However, even when symptoms begin to appear, they are commonly accepted as normal both because the neuronal hyperexcitability trait is harbored by such a large fraction of society and because the symptoms primarily involve the same cognitive-emotional states that every person may experience from time to time.

Another reason that the neuronal hyperexcitability trait has remained so difficult to identify is that stress-inducing circumstances are highly specific to the individual and, in most cases, only really known by the individual. This makes it difficult to assess the appropriateness of the symptoms to the circumstances that seem to precipitate them. Also, due to the variable time-course of kindling, symptom-onset can be delayed by days, weeks, or months [82], thus adding to the difficulty of assessing the appropriateness of the symptoms.

Yet another reason that the neuronal hyperexcitability trait has remained so elusive is that the diagnosis of psychiatric disorders has traditionally been symptom-based rather than pathology-based. Hence, the signs and symptoms of neuronal hyperexcitability, which can be highly diverse due to the high diversity of neuronal circuits and firing patterns, are generally viewed as different syndromes rather than as exacerbations of a shared neurophysiological abnormality [83, 84]. This, in turn, has treatment implications that can lead clinicians even further down the wrong path due to current prescribing habits. Since the development of the monoamine hypothesis of depression, prescribers have been strongly entrained to treat most psychiatric disorders with antidepressants. However, based on resting vital-sign measurements (the diagnostic value of which will be discussed later), the neuronal hyperexcitability trait is harbored by approximately 4 out of 10 persons [67, 85, 86]. This estimate is corroborated by the fact that anticonvulsants and other brain-calming drugs had, throughout most of recorded history, been the mainstay of medical

treatment for a wide range of emotional and physical ailments [87]. Today, in the wake of the antidepressant revolution, the use of anticonvulsants has been relegated to bipolar spectrum disorder [67, 88]. The problem with this diagnostically-based change is that bipolar spectrum disorder is often misdiagnosed as unipolar depressive disorder [89-92]. This error is further complicated by the fact that antidepressants can have beneficial effects in bipolar spectrum patients despite the fact that they do not address the core physiological abnormality in the disorder [72]. All of these barriers to recognizing the neuronal hyperexcitability trait underscore the need to more easily identify the trait.

VI. TOWARD AN OBJECTIVE METHOD OF IDENTIFYING THE NEURONAL HYPEREXCITABILITY TRAIT

In recent years, an explosion of clinical studies has identified an association between resting vital-sign measurements and the later development of various psychiatric and general medical conditions. In a longitudinal study involving more than one million men in Sweden, Latvala et al. [93] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [94] found that adolescent girls with emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of chronic physical illnesses, including diabetes [95-98], high blood pressure [99-101], cardiovascular disease [102-107], cerebrovascular disease [108-110], cancer [110-112], dementia [113], and all-cause mortality [110, 114]. The subtle vital-sign elevations with which these illnesses are associated are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [115]. This is the MCNH explanation for why the lifespan of persons with severe mental illness tends to be much shorter than the general population [115]. The reason that psychiatric and "functional" physical symptoms would tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal excitation than other organs and systems of the body [116]. The physical consequences would tend to be delayed because they would express the gradual erosive effects of neuronal hyperexcitability, which can take years or even decades to occur [115]. Thus, there is mounting evidence that the neuronal hyperexcitability trait can be identified objectively [67, 115]. It has been estimated that, in the absence of any significant cardiorespiratory disease, confounding medications, or substances of abuse, an RHR above 75

beats/min or an RRR above 15 breaths/min is indicative of the neuronal hyperexcitability trait. Parenthetically, in the more than 100 consecutive outpatients that have been studied thus far, resting heart and respiratory rate measurements have proven to be more sensitive in detecting the neuronal hyperexcitability trait than formal clinical assessments.

VII. DISCUSSION

The goal of this review was to address the question that every behavioral health clinician faces—that of deciding whether a patient should be treated with psychotherapy, medical therapy, or a combination of the two. Short of an objective way for either the patient or the clinician to make this determination, self-referral is generally the decisive factor in determining which type of therapy a patient receives, at least initially. As discussed earlier, this is potentially faulty because most patients have limited insight into the psychophysiological underpinnings of their distress, and even experienced clinicians are often unable to tell how much of the patient's distress is rooted in psychological factors and how much is rooted in biological factors. However, the idea that the inherited trait of neuronal hyperexcitability can drive the same symptoms as purely psychological factors, taken together with the idea that the trait can be identified through resting vital-sign measurements, has the potential to objectivize, for the first time, which type of therapy—psychological or biological—a patient should receive. It also has the potential to determine what percentage of patients who present for behavioral health services are carriers of the neuronal hyperexcitability trait.

Under the current system of referral and treatment selection, many patients may be receiving the wrong type of therapy. Some may be receiving psychotherapy when they should be receiving medical therapy, and some may be receiving medical therapy when they should be receiving psychotherapy. There may also be some who are receiving one form of therapy or the other when in fact they should be receiving both forms of therapy simultaneously. Also, because the neuronal hyperexcitability trait continues to be so elusive, some patients may be receiving the wrong type of medication [71, 87, 117].

Fortuitously, all of this could be about to change with the growing recognition that resting vital-sign measurements offer an objective way to determine which form of treatment a patient should receive. Beyond that, recognizing neuronal hyperexcitability as the core abnormality in mental illness could bring with it a highly treatable biological target. This too would be a first in psychiatry because the current system of diagnosis and treatment is symptom-based rather than pathology-based. Guided by the MCNH hypothesis, any patient who was determined, based on resting vital-sign

measurements, to have a hyperexcitable brain could first be educated about the natural ways to calm the brain, such as stress reduction, establishment of an early sleep schedule, regular exercise, and the other lifestyle habits that were discussed earlier. Patients with moderate-to-severe symptoms could also be offered anticonvulsant therapy, as the degree of improvement achieved through lifestyle changes alone is typically limited to about 20%. Anticonvulsants, which, based on their putative mechanism of action, could more aptly be called “neuroregulators” [118], go right to the root of the problem. They reduce the excitability of the neurological system, thereby compensating for the gene abnormality that is believed to underlie the neuronal hyperexcitability trait. Moreover, unlike commonly prescribed medications, such as antidepressants, psychostimulants, and antipsychotics, all of which alter the activity of specific receptors and circuits in the brain, neuroregulators simply normalize brain function. This is a healthier approach because the brain, in most of the common psychiatric disorders, is not misfiring but rather over-firing. Hence, if a given neuroregulator were ineffective at reducing symptoms, it could appropriately be replaced with another neuroregulator rather than switching to a different class of drugs; and if one neuroregulator were only partially effective, a second one could be added, and so on. This approach, which could be called “focused neuroregulation” [119], would optimize the effectiveness of neuroregulators and minimize the need for medications that can have unpredictable, conflicting, and sometimes paradoxical effects [7, 72, 117]. As for those patients whose resting vital signs fell below the minimum cutoffs, psychotherapy alone could be recommended as first-line treatment. In such cases, the therapy would be addressing a problem that was fundamentally psychological rather than just helping a patient cope with a problem that was fundamentally neurological. Thus, the MCNH hypothesis in conjunction with resting vital-sign measurements has the potential to fast-track patients to the most efficient and effective treatment approach. Moreover, because resting vital signs can be measured in the comfort of one's own home, prospective patients would be able to perform the initial screening themselves. In an era of cellphones, smart watches, and a host of new health-tracking devices, this triage system could not be any easier or more practical.

VIII. DIRECTIONS FOR FUTURE RESEARCH

Urgently needed are clinical studies aimed at determining the effectiveness of focused neuroregulation in those patients who, irrespective of their DSM diagnosis, present with an RHR above 75 beats/min or an RRR above 15 breaths/min. This approach would allow researchers to circumvent the problem of overlapping and co-occurring diagnoses

and focus on determining which psychiatric symptoms would be most responsive to focused neuroregulation. A high response rate would help validate the use of resting vital-signs as markers of neuronal hyperexcitability. Also, by calculating the fraction of patients who exceed the resting vital-sign cutoffs, insight could be gained into the epidemiology of neuronal hyperexcitability and the sensitivity of resting vital-sign measurements as biomarkers of the neuronal hyperexcitability trait. If promising, such pilot studies could be followed by head-to-head prospective studies comparing the short and long-term effectiveness of this objectively-based method of diagnosis and treatment to standard (symptom-based) treatment.

Additionally, because resting vital signs appear to be constitutionally elevated in carriers of the neuronal hyperexcitability trait [93], prevention studies could be done to determine the benefits of prophylactic neuroregulator therapy in those members of severely affected families who have upper-end-of-normal resting vital signs but have not yet manifested any clear evidence of mental illness. Adjustments of prophylactic medication in such persons could be guided by the response of resting vital signs to the medication and by reassessing for signs and symptoms that may become more clinically apparent only after they are reduced. Also in these studies, the relative importance of resting vital signs as predictive markers of mental illness and the specificity of these markers could be determined by tracking the progress of siblings whose vital signs fell below the hypothesized cutoffs as well as those whose resting vital signs fell above the hypothesized cutoffs but who decided against prophylactic therapy.

Finally, to validate the hypothesis that the vulnerability to developing any of a wide range of psychiatric and functional physical symptoms is rooted in polymorphisms of single gene loci, comprehensive family diagnostic studies could be performed to determine the inheritance pattern of these symptoms and their associated psychiatric disorders as a clinically heterogeneous but genetically related group. A classic Mendelian distribution would provide further support for the MCNH hypothesis and potentially pave the way for future research using CRISPR-Cas9 technology [120], offering exciting possibilities for targeted gene therapies [121].

IX. CONCLUSION

By recognizing the cognitive-emotional system as a dynamic interplay between mind and brain and reconceptualizing psychiatric symptoms as pathological hyperactivity in symptom-related circuits in the brain, the MCNH hypothesis, in conjunction with resting vital-sign measurements, has the potential to revolutionize the treatment of mental illness. Rather than treating patients based on subjective assessments and personal skill

sets, treatment selection could, for the first time, be based on quantitative biomarkers. Resting vital-sign measurements provide an objective, evidence-based, and easily accessible way to identify the neuronal hyperexcitability trait, an inherited neurophysiological abnormality that is hypothesized to be at the root of most psychiatric and functional physical symptoms. In addition to improving diagnostic accuracy and guiding treatment selection, targeting the neuronal hyperexcitability trait informs the use of focused neuroregulation, a safer, faster, and more effective treatment approach for those patients who are determined, based on resting vital-sign measurements, to have a biologically-based psychiatric disorder. By identifying the neuronal hyperexcitability trait, the challenge of overlapping and co-occurring psychiatric diagnoses is circumvented and the use of medications that have unpredictable, conflicting, and sometimes paradoxical effects can be minimized. Targeting the neuronal hyperexcitability trait also has the potential to ward off psychiatric symptoms before they even begin and reduce the risk of developing any of the wide range of chronic health conditions with which this highly prevalent trait has been associated. In short, the MCNH hypothesis, in conjunction with resting vital-sign measurements, has the potential to change the face of modern psychiatry by transforming the treatment of mental illness from a symptom-based practice to a biologically-based practice. By seizing this unprecedented opportunity, we can strive toward a future in which behavioral healthcare, like other fields of medicine, is aimed at specific pathological processes, thus streamlining care, speeding recovery, and overcoming the long-held stigma of mental illness.

Conflicts of Interest

The author declares that he has no competing interests.

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Abstract- We report a rare case of Wilson's Disease with neurologic features in a 31-year-old man. This disease consists of a disturbance of copper metabolism secondary to a mutation in the gene responsible for encoding the tissue transporter and the enzyme that incorporates the excess element into bile, generating toxic accumulation in the liver, cornea, and central nervous system. According to his wife, the patient had been treated for an unspecified mood disorder. The clinical picture was characterized by depressive mood, anhedonia, and anxiety. He had his first seizure episode on December 3rd, 2021. He progressed with dysarthria, ataxic gait, dystonia of the right-hand flexor muscles, and intermittent urinary incontinence. Marked worsening was observed after the diagnosis of COVID-19 in February 2022. At the clinical evaluation on March 24th, risorius muscle dystonia (risus sardonicus), resting tremor, and Kayser Fleischer rings at slit-lamp examination was also noted.

Keywords: wilson disease. inborn errors in metal metabolism. dystonia.

GJMR-A Classification: NLM: WL 350



NEUROLOGICAL WILSON DISEASE IN A YOUNG BRAZILIAN ADULT CASE REPORT

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Neurological Wilson Disease in a Young Brazilian Adult: A Case Report

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Abstract- We report a rare case of Wilson's Disease with neurologic features in a 31-year-old man. This disease consists of a disturbance of copper metabolism secondary to a mutation in the gene responsible for encoding the tissue transporter and the enzyme that incorporates the excess element into bile, generating toxic accumulation in the liver, cornea, and central nervous system. According to his wife, the patient had been treated for an unspecified mood disorder. The clinical picture was characterized by depressive mood, anhedonia, and anxiety. He had his first seizure episode on December 3rd, 2021. He progressed with dysarthria, ataxic gait, dystonia of the right-hand flexor muscles, and intermittent urinary incontinence. Marked worsening was observed after the diagnosis of COVID-19 in February 2022. At the clinical evaluation on March 24th, risorius muscle dystonia (risus sardonicus), resting tremor, and Kayser Fleischer rings at slit-lamp examination was also noted. Cerebrospinal fluid exam without abnormalities. Imaging workup revealed signaled alteration in bilateral putamen, midbrain, and pons. Laboratory tests revealed mild impairment of liver function and abdominal ultrasound with no evident abnormalities. Specific tests confirmed the diagnosis (serum copper and 24-hour urine copper levels elevated and reduced serum ceruloplasmin). This case report represents the importance of a detailed neurological clinical evaluation and the association of findings with imaging and laboratory workup. It is a rare disease whose epidemiology in Brazil lacks data, and complementary tests have reduced specificity. Early diagnosis and treatment have an impact on the neurological prognosis.

Keywords: wilson disease. inborn errors in metal metabolism. dystonia.

I. INTRODUCTION

Wilson's Disease (WD) is a metabolic disorder resulting from biallelic mutations in the ATP7B gene on chromosome 13^{1,2,3} of autosomal recessive inheritance³, characterized by the toxic accumulation of this element in the liver, cornea, and central nervous system⁴.

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The incidence of these mutations in newborns was estimated at 1:7,000 in Sardinia, Italy⁵ and 1.7:100,000 in the Republic of Ireland⁶, in contrast, the prevalence of the disease has been estimated to be between 1:250,000 and 1:300,000 in Sweden and between 1:30,000 and 1:40,000 in other populations⁷.

Copper is an essential cofactor for several enzymes⁸ and is present in foodstuffs such as seafood, pulses, and nuts⁹. Its metabolism is dependent on the ATP7B gene, which is responsible for encoding ceruloplasmin, and on the ATPase, which incorporates it into the bile and allows its exteriorization with the feces^{10,11}.

Due to the absence of these mechanisms, copper accumulates in the liver until it spills over into the bloodstream. High levels of cupremia cause disruption of the blood-brain barrier and deposition with a cytotoxic effect in the striatum, globus pallidus, locus coeruleus, substantia nigra, and cerebral cortex^{4,12}.

II. CASE REPORT

A 31-year-old male, mixed race, bricklayer, residing in Paraisópolis, Minas Gerais State, Brazil. History of alcoholism and drug use. Diagnosis of previous unspecified mood disorder and using Fluoxetine 40mg/day. No other relevant environmental exposures were reported. Report of a male adult family member diagnosed with liver failure of unknown etiology.

Magnetic Resonance Imaging (MRI) of the brain on December 1st, 2021, showed involvement of the putamen, associated with hemosiderin residue, and crus posterius bilaterally, in addition to the midbrain and pons, without restriction to diffusion (images 1A-1D), and an extra-axial parietal left paramedian contrast-enhanced lesion suggestive of meningioma (images 1E-1F). On December 3rd, 2021, the patient suffered the first generalized clonic tonic seizure while sleeping, and in a follow-up visit on December 21st, he started to use Levetiracetam orally.

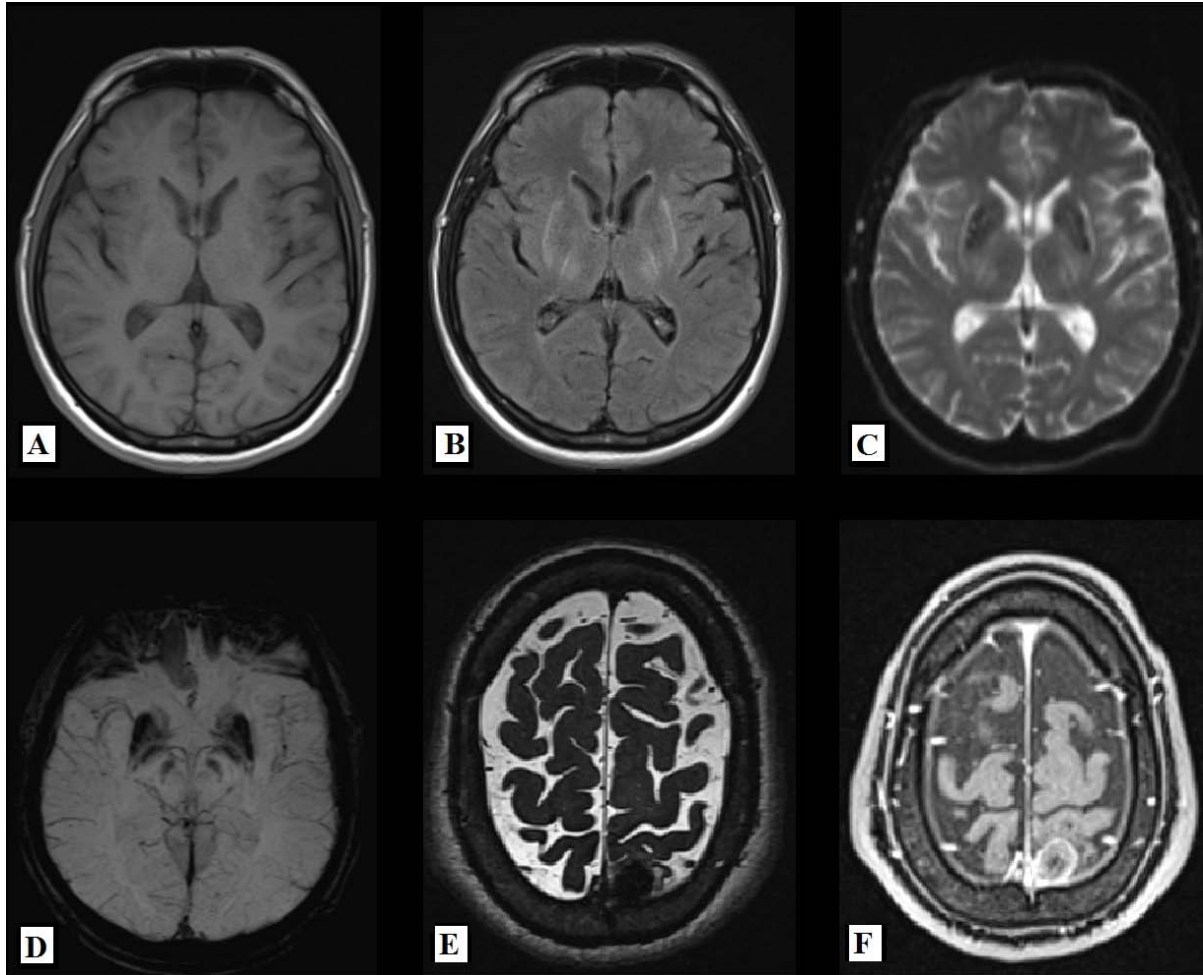
He was diagnosed with Covid 19 on February 3rd, 2022, with a mild evolution without the need for ventilatory support or complications. The wife noted that the development of the disease was accentuated after the infection. From February 9th, he appeared to have speech and gait disturbance, difficulty mobilizing the right hand, and urinary incontinence.

On February 16th, he attended the consultation with the responsible physician who, associated the symptoms with the anticonvulsant and switched to Phenytoin 100mg twice a day and associated Dexamethasone orally. It evolved five days later with intermittent hiccups and prostration that lasted approximately three days.

Cerebrospinal fluid (CSF) collected On March 21st revealed a cell count of 0 unit; glucose 89 mg/dL,

lactate 15.7 mg/dL, gram without staining bacteria, and CSF culture without bacterial growth.

He was hospitalized on March 24th for social reasons to collect WD screening tests. The patient presented to the neurological examination with regular general condition, good spatial orientation, alertness, Glasgow Coma Scale 15, hypomimia, cranial nerve pairs exam without abnormalities, isochoric pupils, normal extrinsic ocular

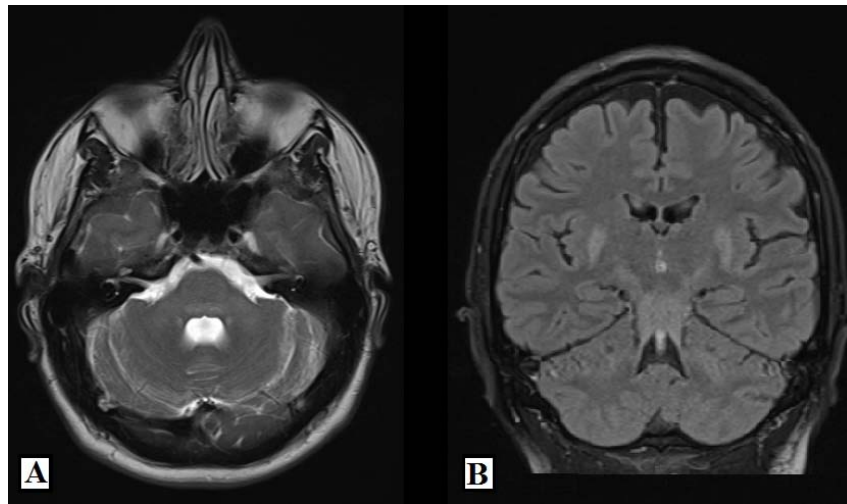


motricity, risus sardonicus, deep tendon reflexes 2/2, muscle strength 5/5 in all testable upper and lower limb muscle groups, somaesthesia, right-hand flexor dystonia, and ataxic gait. Upon slit lamp examination, the presence of Kayser-Fleischer rings was noted.

Laboratory workup of March 24th revealed aminotransferase (AST) 37 mg/dL, alanine aminotransferase (ALT) 35 mg/dL, total bilirubin test 1,00 mg/dL, albumin test 3,7 mg/dL, international normalized ratio (INR) 1,17, and platelets 88×10^9 /L. Tests for disorders of Copper metabolism of the same date revealed total serum copper 24,6 mg/dL (reference range (RR) 70mg/dL-150mg/dL), serum ceruloplasmin 7,0 mg/dL (RR 20mg/dL-60mg/dL) and, finally, 24-hours urine copper test 187,4 mg/dL (RR 70mg/dL-150mg/dL). Child-Pugh, Fibrosis-4, and APRI scores were, respectively, 5 points (Child Class A - least severe

liver disease); 1,99 (undetermined), and 1,11 (significant fibrosis most likely, cirrhosis undetermined). Abdominal ultrasound exam of April 8th, 2022, indicates chronic liver disease with signs of portal hypertension, splenomegaly, and moderate ascites. Electroneuromyography of March 14th, 2022, was absent abnormalities.

During outpatient follow-up, a new MRI of the brain was requested on April 1st, 2022, which denoted better characterization of foci of signal alteration in cerebellar peduncles (images 2).



On June 2022, he had moderate dysarthria, hypomimia, right-hand flexor dystonia, tetraparesis, bradykinesia, and postural instability, but without rigid or resting tremors.

The specific treatment was started on May 2022 with pyridoxine chlorhydrate 50 mg daily and zinc sulfate heptahydrate 4 mg/mL 15mL three times a day orally. Due to the cost of the drug, the patient delayed starting penicillamine.

III. DISCUSSION

Incipient neurological symptoms are subtle and nonspecific, such as difficulty concentrating and motor coordination and handwriting changes (for example, micrograph) ¹³⁻¹⁹ and begin on average between 20 and 40 years ²⁰⁻²². As it progresses, more prominent symptoms appear, whose order of incidence is dysarthria (57.6%), dystonia (42.4%), abnormal gait (37.8%), tremor (36.2%), parkinsonism (17.3%), choreoathetosis (15.3%) and convulsion (4.7%) ^{16,17}. Neurological impairment occurs about a decade after liver failure and, therefore, signs of advanced disease ²³. Cognitive impairment is considered rare and was reported by Machado, Chien, Deguti, et al. (2006)¹⁶ in 4.2% of cases.

Given the heterogeneity of clinical manifestations, the neurological phenotype of WD can be grouped for didactic purposes into dystonic, pseudosclerotic, parkinsonian, and hyperkinetic subtypes ⁴. The patient discussed in this study had a predominance of the dystonic subtype manifested by multifocal dystonia affecting both the risorius muscle (sardonic laughter) and the flexor muscles of the right hand fingers. As reported by Lorincz (2010) ²⁴, bilateral putaminal lesions were found on an MRI of the brain.

Dysarthria can result from any condition that damages the motor control structures necessary for speech production, such as cranial nerves IX, X, XII, cerebellum, and basal ganglia ¹². In this case, it was noted evident bilateral impairment of the basal ganglia.

Seizures are not uncommon and are reported variably in 4.7% ^{16,17} to 14.5% ²⁵ of WD cases. The patient in question presented, at the initial manifestation, a single episode of generalized tonic-clonic seizure without recurrence.

We also detected the presence of brownish Kayser Fleischer rings, more evident in the lower region of the iris bilaterally. Such a semiological sign is due to copper deposition in the Descemet's membrane of the cornea ²⁶ and is present in approximately 100% of neuropsychiatric WD cases ¹⁰.

Psychiatric symptoms are reported by about 30% to 60% of individuals affected by WD ²⁶. In this case, the disorder for which the patient had been using Fluoxetine was not specified. However, the familiar states that at the time of initiation of therapy, he had a depressive mood, anhedonia, and anxiety.

It is possible that such symptoms were already an incipient manifestation of central nervous system involvement.

Cognitive impairment is initially mild and recognized only by family members. It is categorized into frontal lobe syndrome, which involves impulsivity, promiscuity, apathy, hypotenacity, impaired social judgment, planning dysfunction, and emotional lability, and subcortical dementia characterized by slowed thinking amnesia, and executive dysfunction, but without aphasia, apraxia, or agnosia ¹⁰. In this case, it was impossible to attribute a clinical syndrome related to the metabolic disorder, given the history of alcoholism and use of narcotics.

IV. CONCLUSION

This case report represents the importance of a detailed neurological clinical evaluation and the association of findings with Imaging and laboratory workup. It is a rare disease whose epidemiology in Brazil lacks data, and complementary tests have reduced specificity.

Disclosure statement

No potential conflict of interest was reported by the authors.

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A Case of GM 1 Gangliosidosis Type 2 Mimicking Zellweger Syndrome

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Keywords: GM1 gangliosidosis; lysosomal storage disease; beta-galactosidase.

GJMR-A Classification: NLM: WL 17, D009190 ACM: I.2.1



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A Case of GM 1 Gangliosidosis Type 2 Mimicking Zellweger Syndrome

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Abstract- Juvenile GM1-gangliosidosis, also known as type II or juvenile GM1-gangliosidosis, is an autosomal recessive lysosomal storage disorder that clinically differs from infantile GM1-gangliosidosis in the absence of the characteristic cherry-red patch and hepatosplenomegaly. The disease is characterized by mild skeletal abnormalities and slowly progressing neurodegeneration. Due to the late age of onset and unusual presentation, diagnostic confusion with other ataxic and purely neurological disorders is common. There are currently 3–4 recognized types of GM1-gangliosidosis, with type I being the most prevalent phenotype with an average onset age of 6 months. Several subtypes of GM1-gangliosidosis are caused by mutations in the GLB1 gene, but the location and type of deleterious mutations have a direct impact on the severity of the disease and the age at which it manifests. A fully immunized 8-month-old male presented to our hospital with complaints of mild feeding difficulty, periorbital edema, and fever. Facial dysmorphism, hypotonia, delayed development, and hepatomegaly were observed in the patient. As there is currently no effective treatment for GM1 gangliosidosis, the carrier of the disease receives only symptomatic and palliative care. Given that genetic counseling is now the only means of preventing the disease, early diagnosis is crucial.

Keywords: GM1 gangliosidosis; lysosomal storage disease; beta-galactosidase.

I. INTRODUCTION

For cells to function efficiently, the processes of glycoconjugate production and degradation need to be carefully controlled. Glycoconjugates are essential for the majority of biological processes. -galactosidase, also known as GAL, is a lysosomal hydrolase that is responsible for the degradation of a wide variety of glycoconjugates. This is accomplished by hydrolyzing the non-reducing end of glycan moieties. This enzyme's primary role is to delink galactose residues from one another. According to research [1, 2], GM1 ganglioside and its asialo derivative GA1 have a tendency to concentrate in the lysosomes that are

present in brain tissue. The clinical signs of the illness are caused by neurodegenerative pathways in the brain that are triggered when there is an excess of ganglioside—Galactosidase substrate. The accumulation of GM1 gangliosides in microglial cells of the central nervous system has been demonstrated to result in greater activation and infiltration of inflammatory cells into these cells, according to studies conducted using animal models. Previous research [3] has shown that inflammation seems to have a key role in both the etiology of the disorder as well as the neurological symptoms of the condition. It is believed that GM1 gangliosidosis affects between 1 in 100,000 and 200,000 neonates [4]. These numbers are based on estimates from previous studies. Type II GM1 gangliosidosis, sometimes called juvenile or late infantile GM1 gangliosidosis, is distinguished by the slow onset and progression of clinical signs. Ataxia is often the first obvious symptom associated with this subtype, followed by dystonia and spasticity. People who have type II GM 1 gangliosidosis do not have the usual signs of hepatosplenomegaly, cherry red patches, or distinctive facial characteristics. This makes it challenging to make an accurate diagnosis of the condition. People who have this syndrome seem to develop normally in the early stages of the illness. However, symptoms often begin to manifest between the ages of 3 and 5 in those affected by the juvenile form, but they appear sooner in those affected by the late infantile variety. The clinical appearance of GM1 gangliosidosis type II is characterized by diminished neurodevelopmental abilities, including motor and verbal skills. This is one of the disease's defining characteristics. Those who are affected may also have seizures that are difficult to control, which is another potential symptom. Previous research [5] has uncovered conclusions that are comparable to this one. Although the patient had an atypical clinical appearance, it was more suggestive of Zellweger syndrome than anything else. Zellweger syndrome is a hereditary condition that may be identified by the presence of peroxisome deficits. Hypotonia, often known as a loss of muscular tone, and weak or nonexistent vocalizations are two of the hallmarks of this condition, which is frequently brought on by mutations in the PEX gene. Infants affected by this disorder often struggle to feed and may experience the development of seizures at an earlier age.

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II. ETHICAL APPROVAL

The patient's mother consented to the publication of this deidentified case report. Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

III. CLINICAL SUMMARY

We describe a case of an 8-month-old baby who was identified as having Type 2 GM-1 Gangliosidosis. After an uneventful first pregnancy, the patient was the third child of the consanguineous, healthy parents. His older sister appears to be completely normal. The patient had an inguinal hernia, which was discovered during the prenatal ultrasound screening. The patient was once sent to the hospital at the age of 2 months for a hernia operation, during which it was discovered that he had breathing problems. However, with proper measures the surgical procedure

was conducted and the patient was shifted to the ICU for a day. Gradually the patient became better with continuous nebulization and was finally discharged. At 8 months of age, the patient's parents again reported to the hospital with complaints of difficulty in breathing, periorbital puffiness and fever since 3 days in the child. The mother also noticed that the baby was having difficulty in sucking milk and drinking and used to intermittently stop feeding. An increased incident of sweating was observed in the baby while feeding. Upon taking the history, it was revealed that the baby had a running nose and history of cough at 5 months of age for which he had taken treatment from a pulmonologist. Upon examination, it was found that the infant showed clinical signs of pneumonia, bilateral hydrocele, macrocephaly, dolichocephaly, frontal bossing, hypotonia, rickets, and global developmental delay [FIGURE 1] A Zellweger syndrome suspect was identified.



Morphological features of the face and exhibition of hypotonia

The infant was found to have bilateral enlarged kidneys and hepatosplenomegaly upon abdominal examination. There was also a slight ascites present. The brain's magnetic resonance imaging (MRI) revealed widespread corpus callosum thinning, moderately dilated bilateral occipital horns, and insufficient myelination in parieto-occipital white matter. The infant screened positive for rickets, bicytopenia, and severe anaemia in the lab. He had stage 2 hypotension, a well-functioning dilated left ventricle, mild pericardial

effusion, and bilateral pleural effusion, according to his echocardiography. The patient's symptoms were controlled while a confirmative diagnosis was made through gene testing.

A homozygous single base pair deletion in exon 10 of the GLB1 gene, which causes a frameshift and an early truncation of the protein 11 amino acids downstream to codon 327, was discovered, according to the gene report. Another homozygous 2-base pair deletion in exon 11 of the CEP41 gene was discovered

[FIGURE 2], which causes a frameshift and an early truncation of the protein downstream of codon 346. The mutation in the CEP41 gene may be significant, but the gene testing reports classify it as a variant of unknown

importance because it is placed in the gene's last exon and its impact on protein alteration cannot be predicted. There was a dearth of literature supporting this variety.

Gene transcripts showing various variations

Gene# (Transcript)	Location	Variant	Zygoty
GLB1 (-) (ENST00000307363.10)	Exon 10	c.979del (p.Gln327SerfsTer11)	Homozygous

ADDITIONAL FINDINGS: VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

Gene# (Transcript)	Location	Variant	Zygoty
CEP41 (-) (ENST00000675138.1)	Exon 11	c.1036_1037del (p.Asn346LeufsTer?)	Homozygous

Gene Transcript	Location	Variation	Zygoty
GLB1(-) (ENST0000030763.10)	Exon 10	c.979del (p.Gln327SerfsTer11)	Homozygous

Gene Transcript	Location	Variation	Zygoty
CEP41(-) (ENST00000675138.1)	Exon 11	C.1036_1037del (p.Asn346LeufsTer)	Homozygous

IV. DISCUSSION

In this particular instance, there are a few aspects that should be brought to the forefront. The diagnosis of GM-1 Gangliosidosis Type 2 was arrived at after taking into account the clinical phenotype in addition to specific laboratory and genetic abnormalities. The condition known as juvenile GM1 gangliosidosis, which is passed down in an autosomal recessive manner and results in neurological regression in those who are affected by it, was just described. Patients affected by GM1 gangliosidosis type I begin to display clinical symptoms within the first month of their lives. People who have GM1 gangliosidosis type II continue to reach their typical neurodevelopmental milestones (juvenile form) until late infancy (late infantile form) or late childhood. This is the case even in the juvenile form. Because of this, treatment options for diseases with a later onset, such as enzyme replacement therapy, cell therapy, and bone marrow transplantation, can be more successful if molecular diagnosis is performed early on in pre-symptomatic individuals who have a positive family history. There is currently no simple biochemical test available that can be used for carrier screening in high risk people and their families [6]. It has been reported in the past that

patients with type II diabetes have an enzyme activity level that is affected less severely [7]. The GM1 gangliosidosis type II and the discovered mutation in the GLB1 gene appear to be completely correlated with one another, with 100 percent phenotypic plasticity in individuals who are homozygous for the mutation. In spite of the fact that heterozygous carriers for this mutation do not appear to be suffering from any symptoms of illness, there is a risk that they will pass on the deleterious mutation to their offspring. As a consequence of this, people who have had childhood ataxia and the relatives of patients who are already well-known should get a GLB1 genetic test before getting married consanguineously. Consanguineous marriage, a family history of deaths with similar symptoms, increasing ataxia, and neurodevelopmental regression are all factors that assist medical professionals in narrowing down the list of possible alternative diagnoses and advising patients on the most appropriate genetic tests.

V. CONCLUSION

Juvenile GM1 gangliosidosis type II was shown to have an autosomal recessive variant caused by a missense mutation in the GLB1 gene in our patient. The

mutation is a rare previously reported pathologic mutation along with the mutation in CEP41 gene. The significance of the later gene's mutation in the illness of the patient is yet to be discovered.

Our findings support a connection between juvenile gangliosidosis type II patients' ataxia and neurodegeneration and the GLB1 gene mutation.

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PREFERRED AUTHOR GUIDELINES

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

We typeset manuscripts using advanced typesetting tools like Adobe In Design, 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.

Alternatively, you can download our basic template from <https://globaljournals.org/Template>

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

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Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

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3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
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7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

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- Any other original work

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The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

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.

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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).

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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 through 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.
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- 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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