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CONTENTS OF THE ISSUE

i. Copyright Notice
ii. Editorial Board Members
iii. Chief Author and Dean
iv. Contents of the Issue

2. Literature Evidence and Arrive Assessment on Neuroprotective Effects of Flavonols Quercetin, Rutin and Isoquercitrin in Neurodegenerative Diseases’ Models. 7-16
3. Cerebellar Dysplastic Gangliocytoma as the First Presentation of Cowden Syndrome. 17-22
4. The Benefits of Neuroids/Neuropeptides in Combating Cerebrovascular, Neurological and Ocular Diseases. 23-26

v. Fellows
vi. Auxiliary Memberships
vii. Process of Submission of Research Paper
viii. Preferred Author Guidelines
ix. Index
Case Report: Posterior Reversible Encephalopathy Syndrome in a Paediatric Patient as First Presentation of Thrombotic Thrombocytopenic Purpura

By Abdullah Alasaad, Roaa Amer & Eman Bakhsh
King Saud Bin Abdulaziz University

Abstract- Posterior reversible encephalopathy syndrome (PRES) usually presents with rapid onset of neurologic symptoms with characteristic vasogenic oedema in imaging studies. PRES is most importantly associated with hypertension and kidney disease. We describe a case of PRES in a 13-year-old female patient who presented with normal vital signs, neurological symptoms, oliguria, and laboratory test results consistent with thrombotic thrombocytopenic purpura (TTP). Head computed tomography (CT) scan revealed subtle hypodensity in the white matter of the right parietal lobe, strongly suggesting PRES, with multiple hemorrhagic foci in the right frontal lobe and right basal ganglia. Aggressive TTP treatment was initiated; however, she developed rapidly progressive glomerulonephritis and renal failure. Twelve days since presentation, she developed severe acute respiratory distress, which resulted in death. Therefore, PRES need not be a complication; it can be the presenting sign of an undiagnosed disease and a high index of suspicion is required in such cases.

Keywords: posterior reversible encephalopathy syndrome, thrombotic thrombocytopenic purpura, seizures, hypertension, renal failure, paediatrics, vasogenic oedema, renal failure, headache, oliguria.

GJMR-A Classification : NLMC Code: WL 141.5, WH 315

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Case Report: Posterior Reversible Encephalopathy Syndrome in a Paediatric Patient as First Presentation of Thrombotic Thrombocytopenic Purpura

Abdullah Alasaad α, Roaa Amer α & Eman Bakhsh ρ

Abstract- Posterior reversible encephalopathy syndrome (PRES) usually presents with rapid onset of neurologic symptoms with characteristic vasogenic oedema in imaging studies. PRES is most importantly associated with hypertension and kidney disease. We describe a case of PRES in a 13-year-old female patient who presented with normal vital signs, neurological symptoms, oliguria, and laboratory test results consistent with thrombotic thrombocytopenic purpura (TTP). Head computed tomography (CT) scan revealed subtle hypodensity in the white matter of the right parietal lobe, strongly suggesting PRES, with multiple hemorrhagic foci in the right frontal lobe and right basal ganglia. Aggressive TTP treatment was initiated; however, she developed rapidly progressive glomerulonephritis and renal failure. Twelve days since presentation, she developed severe acute respiratory distress, which resulted in death. Therefore, PRES need not be a complication; it can be the presenting sign of an undiagnosed disease and a high index of suspicion is required in such cases.

Keywords: posterior reversible encephalopathy syndrome, thrombotic thrombocytopenic purpura, seizures, hypertension, renal failure, paediatrics, vasogenic oedema, renal failure, headache, oliguria.

I. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a complication with various medical conditions which usually presents with rapid onset of neurological symptoms such as seizures, altered mental status, and visual disturbances (Hobson et al, 2012). It was initially believed to be associated with eclampsia, post-transplant use of cyclosporine, and acute hypertension (Bartynski, 2008). Further studies showed a relationship between PRES and hypertension, immunosuppressive drugs, and post-transplant status, and autoimmune and vascular diseases, which are mostly found in patients with renal diseases (Hobson et al, 2012). Furthermore, PRES is a clinicoradiological syndrome characterized by its unique symptoms and pathognomonic radiological findings (Bartynski, 2008). Here, we present a case of PRES in a patient with clinical and laboratory evidence of thrombotic thrombocytopenic purpura who developed severe acute renal dysfunction in the absence of hypertension. Although the standard treatment was initiated, the patient died due to severe respiratory distress.

II. Case Report

A 13-year-old female patient presented to the emergency department with nausea, vomiting, headache, confusion, seizures, and oliguria. She had no significant past medical history and no previous similar episodes were reported. Family history was unremarkable, with no evidence of any blood disorder in the family. On initial examination, the patient looked dehydrated and somnolent with a Glasgow coma scale score of 10. Vital signs, including blood pressure, were within normal limits on different occasions.

The patient underwent a head computed tomography (CT) scan to assess the extent of the neurological pathology, which demonstrated multiple subcortical hypodensities in the right frontal and parietal lobes, highly suggestive of PRES, as well as multiple well-defined hyperintensities in the right frontal lobe and right basal ganglia, suggesting multiple haemorrhagic foci (Figure-1A, and 1B).

Initial blood workup showed anaemia (haemoglobin 7 mg/dL), thrombocytopenia (40,000 mg/dL), high erythrocyte sedimentation rate (160 mm/hour), and high C-reactive protein (20 mg/L) levels. Additionally, signs of haemolysis such as high lactate dehydrogenase (900 IU/L) and bilirubin (5 mg/dL) levels were also present. Further laboratory tests assessing renal functions showed normal serum creatinine (80 umol/L) and glomerular filtration rate (GFR) (98 ml/min/1.73m²). Serology tests revealed a positive perinuclear antineutrophilic cytoplasmic (p-ANCA), anti-glomerular basement membrane (anti-GBM), and antimyeloperoxidase antibodies. A lumbar puncture was performed to exclude infectious causes and it showed normal coloured cerebrospinal fluid with normal cell and protein counts. Polymerase chain reaction assays for
herpes-simplex virus, cytomegalovirus, and Epstein-Barr virus were negative.

Targeted treatment for the underlying cause was delayed due to the haemodynamic instability. After the patient was stabilized, a diagnosis of thrombotic thrombocytopenic purpura (TTP) was suspected based on laboratory results. Subsequently, the patient was started on 500 mg/day intravenous methylprednisolone and 30 mg/day oral prednisolone, and she underwent multiple plasma exchange procedures along with infusions of fresh frozen plasma. Due to the suspicion of TTP, genetic testing was done. However, the results were not available at the time as it required 5 days. After 10 days, a follow-up brain MRI showed bilateral parietal high signals on FLAIR sequence and diffusion ADC map (figure-2A and 2B). MR angiography showed patent posterior cranial circulation.

Despite the active treatment for TTP, the patient developed rapidly progressive glomerulonephritis; the GFR drastically decreased to 6 ml/min/1.73m² and serum creatinine was extremely high at 657 umol/L. Histopathological examination of the renal biopsy revealed glomerular crescent formation with linear IgG, IgA, IgM, and C3 deposits on the glomerular capillary walls. The patient was started on dialysis immediately.

Dialysis was continued for the patient, with no significant improvements in the first 5 days. Unfortunately, the patient’s family refused any further investigations or interventions because they had not seen any improvement since her first presentation. Twelve days after her initial presentation, the patient developed severe acute respiratory distress, which resulted in death. Postmortem, the results of genetic testing revealed a 70% deficiency in ADAMTS 13 levels.

III. Discussion

PRES is a rare neurotoxic state that is coupled with a rapid onset set of symptoms, most commonly seizures, visual disturbances, headache, and altered mental state (Hobson et al, 2012) and characteristic vasogenic oedema seen in imaging studies (Bartynski, 2008). PRES is also associated with multiple clinical diseases, most importantly hypertension and kidney diseases (Bartynski, 2008; Hobson et al, 2012). In this case, we report the course of a paediatric patient who came to the emergency room with PRES as the first presentation of TTP. PRES has been reported as a complication of TTP before; however, it usually occurs in adults and is considered rare in children with a poor prognosis if early treatment is not initiated (Bhat et al, 2015).

The relationship between the two diseases lies in the pathophysiology of PRES: the first mechanism being theorized as disturbances in the brain’s autoregulation of blood flow caused by hypertension (Hobson et al, 2012), and the other being endothelial dysfunction caused by inflammatory processes (Hobson et al, 2012). These mechanisms explain the association of PRES with many autoimmune diseases such as Henoch-Schonlein purpura (Sivrioglu et al, 2013), scleroderma (Chen et al, 2016), and juvenile idiopathic arthritis (Zhang et al, 2014). Both the processes can be found in TTP due to the formation of microthrombi (Yu et al, 2015).

However, in this case, the diagnosis of PRES was difficult due to multiple reasons. First, TTP can also manifest with neurological symptoms; therefore, the differentiation between PRES and TTP in this case was only possible through imaging studies (Bhat et al, 2015), which could not be obtained emergently due to the patient’s hemodynamic instability. However, brain MRI was performed 10 days later, which showed bilateral parietal high signals on FLAIR sequence and diffusion ADC map. Secondly, although the patient’s laboratory findings are consistent with TTP, she was totally asymptomatic until she developed a seizure. Furthermore, the variable presentations of PRES and the difficulty in diagnosing it (Burrus et al, 2010) led to a delay in the diagnosis and treatment, which should have been commenced immediately to prevent permanent neurological damage, similar to what happened in this case (3).

Additionally, the presence of PRES in paediatric patients with TTP is uncommon. However, when discussing the risk factors and their correlation to PRES in general, hypertension plays a pivotal role. Recent studies on the correlation of TTP and PRES among paediatric population have shown the presence of hypertension in 100% of the patients with PRES (Bhat et al, 2015). Nevertheless, significant correlation between the degree of hypertension and PRES could not be established (Bhat et al, 2015; Burrus et al, 2010). The only significant risk factors common to, both, acute TTP and PRES were GFR and worsening renal failure (Burrus et al, 2010) as were seen in this case.

The diagnosis of PRES is based on clinical presentation and radiological findings on CT scan or MRI. In acute settings, CT scan is usually used due to its rapid availability (Hobson et al, 2012); however, CT scan lacks sensitivity and, therefore, normal findings could be seen. MRI, on the other hand, is considered the superior imaging study, but many diverse findings of PRES were not detected on MRI (Hobson et al, 2012). The typical findings on MRI include symmetrical bilateral cortical and subcortical vasogenic oedema in the vascular watershed areas, most commonly in the occipital and parietal regions (Bartynski, 2008; Hobson et al, 2012) followed by the frontal lobes, the inferior temporal-occipital junction, and the cerebellum (Bartynski, 2008). Furthermore, PRES can also show atypical findings on imaging studies such as asymmetrical involvement, haemorrhage, cortical lesions, and the involvement of only the frontal lobe (Hobson et al, 2012). Such atypical
findings were found in this patient in the form of multiple cortical and subcortical hypodensities in the right frontal and parietal lobes, with multiple haemorrhagic foci in the right frontal lobe and right basal ganglia.

Although neuroimaging is not usually done in patients with TTP, it is used in the patients with neurological manifestations to exclude microangiopathic thrombosis or haemorrhage. Recent imaging studies on the findings in patients with acute TTP have revealed that imaging could show signs of PRES, haemorrhage, or acute infarcts. More importantly, they demonstrated that the most common neurological finding among those patients was PRES (Burrus et al, 2009; Yu et al, 2015). Furthermore, the studies also demonstrated that the abnormalities found on imaging studies did not affect the clinical outcomes, irrespective of how extensive they were (Burrus et al, 2009; Yu et al, 2015).

Our recommendations include the following. First, PRES should not be considered as a complication of a disease or a state by itself, as it may reveal itself as the first presentation of an undiagnosed disease. Secondly, in cases of acute TTP with neurological manifestations, PRES should be highly considered since it is the most common imaging finding in such patients. Finally, in those patients, prompt treatment must be initiated as soon as possible, especially in paediatric patients, as it alters the prognosis.

### IV. Conclusion

PRES is a rare neurotoxic state that is coupled with a rapid onset of symptoms. PRES has been reported as a complication of TTP before; however, it usually occurs in adults and it is considered rare in children with a poor prognosis if not treated early. Nevertheless, maintaining a high index of suspicion is warranted, as PRES should not be considered only as a complication of a disease because it may reveal itself as the first presentation of an undiagnosed disease.

### References

Figure 1A: Axial brain non-enhanced CT image showing multiple right frontal and right parietal subcortical hypodensities.

Figure 1B: Axial non-enhanced brain CT image showing focal rounded hyperdensities in the medial aspect of the right frontal cortex consistent with cortical bleeding.
Case Report: Posterior Reversible Encephalopathy Syndrome in a Paediatric Patient as First Presentation of Thrombotic Thrombocytopenic Purpura

Figure 2A: Brain MRI axial FLAIR sequence demonstrating bilateral symmetrical cortical and subcortical high T2 signal in the frontal and parietal lobes

Figure 2B: Axial ADC map showing high ADC signal in the parietal lobes indicating vasogenic oedema
Literature Evidence and Arrive Assessment on Neuroprotective Effects of Flavonols Quercetin, Rutin and Isoquercitrin in Neurodegenerative Diseases’Models

By Ana Carolina Bombardi Duarte, Maycon Giovani Santanai, Gulhermedi Camilo Orfalii, Carlos Tadeu Parisi de Oliveira & Denise Gonçalves Priolli

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Abstract- This paper was based on a literature search of PubMed and Scielo databases using the keywords “Flavonoids, Neuroprotection, Quercetin, Rutin, Isoquercitrin, Alzheimer, Parkinson, Huntington” and combinations of all the words. We collected relevant publications, during the period of 2000 to 2016, emphasizing in vivo and in vitro studies with neurological assessment of flavonol’s potentials, as well as classifying studies according to evidence levels, in order to elucidate evidence-based literature and its application on clinical research. In addition, we highlight the importance of flavonols in modern research fields, indicating their neuroprotective potential and use thereof as preventive and therapeutic treatment of numerous neurodegenerative disease. Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and Huntington's disease, represent worldwide a major health problem with great financial impact. They are multifactorial diseases, hallmarked by similar pathogenesis that covers conditions such as oxidative stress, formation of free radicals, abnormal protein dynamics (degradation and aggregation), mitochondrial dysfunction, lipid peroxidation and cellular death or senescence. Flavonols are polyphenolic compounds, widely distributed in the plant kingdom and found in high concentrations in vegetables, fruits and teas. Their neuroprotective effects are mainly related to their antioxidant, anti-proliferative and anti-inflammatory properties. It was this paper’s intention to contribute with an evidence analysis of recent studies approaching neuroprotective effects of flavonols and the potential to conduct human clinical studies.

GJMR A Classification : NLMC Code: WL 140

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Literature Evidence and Arrive Assessment on Neuroprotective Effects of Flavonols Quercetin, Rutin and Isoquercitrin in Neurodegenerative Diseases’ Models

Ana Carolina Bombardi Duarte a, Maycon Giovani Santana b, Gulhermedi Camilo Orfali c, Carlos Tadeu Parisi de Oliveira d & Denise Gonçalves Priolli e

Abstract- This paper was based on a literature search of PubMed and Scielo databases using the keywords “Flavonoids, Neuroprotection, Quercetin, Rutin, Isoquercitrin, Alzheimer, Parkinson, Huntington” and combinations of all the words. We collected relevant publications, during the period of 2000 to 2016, emphasizing in vivo and in vitro studies with neurological assessment of flavonol’s potentials, as well as classifying studies according to evidence levels, in order to elucidate evidence-based literature and its application on clinical research. In addition, we highlight the importance of flavonols in modern research fields, indicating their neuroprotective potential and use thereof as preventive and therapeutic treatment of numerous neurodegenerative disease. Neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease and Huntington’s disease, represent worldwide a major health problem with great financial impact. They are multifactorial diseases, hallmarked by similar pathogenesis that covers conditions such as oxidative stress, formation of free radicals, abnormal protein dynamics (degradation and aggregation), mitochondrial dysfunction, lipid peroxidation and cellular death or senescence. Flavonols are polyphenolic compounds, widely distributed in the plant kingdom and found in high concentrations in vegetables, fruits and teas. Their neuroprotective effects are mainly related to their antioxidant, anti-proliferative and anti-inflammatory properties. It was this paper’s intention to contribute with an evidence analysis of recent studies approaching neuroprotective effects of flavonols and the potential to conduct human clinical studies.

1. Introduction

Flavonoids represent one of major polyphenolic groups, which are widely distributed in the plant kingdom and commonly found in vegetables, fruits and teas of the human diet1. These compounds have shown low toxicity as well as a variety of physiological effects1. In the past few decades, these naturally occurring compounds have attracted much attention by reported beneficial effects on health, such as antioxidant, antitumor, anti-inflammatory and anti-allergic effects2, as well as presenting low toxicity to human organism3. In midst the various classes of flavonoids, the flavonols have been the focus of many in vitro and in vivo studies for their diversified actions on numerous biological pathways1. Structurally, flavonoids are composed of a basic flavylum cation, with three phenolic rings4. Flavonols present subtle molecular changes to the main ring (Ring C), with the addition of a hydroxyl group (OH) on the third carbon, and a carbonyl group (C=O) on carbon fourth 5. Many reports have shown that structure changes of flavonoid molecules result in variations of bioavailability, by changing absorption efficiency and pathways; thus, also altering biological effects and creating action mechanisms specificity 6–8.

Flavonoids neuroprotective effects are mostly bound to its related antioxidant, anti-proliferative and anti-inflammatory properties9,10. The Central Nervous System (CNS) is highly exposed to oxidative damage, due to high oxygen consumption, high levels of unsaturated lipids and presence of transitional metals1. In addition, because of inefficient antioxidant defense mechanisms, alterations of neuronal organic homeostasis can cause grave repercussions1–9. Antioxidant properties are correlated since oxidative stress and lipid peroxidation have been linked to a range of neurological pathologies, such as brain trauma, ischemia and neurodegenerative disorders 10–12. Thus, flavonoids ability to scavenge ROS and inhibit lipid peroxidation, protecting neuronal cells from oxidative damage, may be used to prevent and treat neurological pathologies 2. Neurodegenerative disorders, such as Alzheimer’s, Parkinson’s and Huntington’s disease cause a progressive functional alteration of neuronal systems13. Worldwide, they present variable incidence and constantly relate to high morbidity rates, higher cost in health care and social impairment13–15. These pathologies have been well studied; however, new advances in physiopathology and therefore, in therapeutic modalities are infrequent, maintaining no cure or reversible treatments.

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Other flavonoids, such as resveratrol, fisetin and hyperin have also been considered as potential drugs with neuroprotective effects\(^9\). Recent studies verified, different flavonoids act on specific organic pathways\(^1\), yet comparable studies between flavonoids are rare. Resveratrol, as an example, has shown neurological and cognitive enhancement properties in a clinical trial\(^{22}\). Quercetin and rutin have been widely investigated as therapeutic drugs, especially concerning anti-proliferative and antioxidant effects, for many diseases, including CNS pathologies. However, neuroprotective potential of flavonoids in human trials has been poorly addressed, and Isoquercitrin has rarely been implied in studies investigating neuroprotective effects and comparison studies of the same subject.

II. Methods/Research

a) Literature Review

This paper was based on a literature search of PubMed and Scielo databases using keyword combinations "Flavonoids+Neuroprotection"; "Quercetin OR Rutin OR Isoquercitrin + Neuroprotection"; "Quercetin OR Rutin OR Isoquercitrin + Alzheimer OR Parkinson OR Huntington", during the period of 2000 to 2016. Clinical trials were assessed in each search. Studies involving flavonoid panel and flavonoid combinations were considered.

b) Literature Evidence

Evidence Based Medicine (EBM) is a systematic analysis of present-day research and scientific findings, in which obtained information is classified by authenticity and Evidence Level results\(^{24}\). Thus creating a hierarchy system to evaluate information and incorporate in a practical environment of research, as well as to support the conduct of clinical care and therapeutic options\(^{26}\). Recommendation levels are the results of extensive research analysis and an important guide to practitioner’s clinical decisions\(^{28}\). Although animal experiments have always contributed to our understanding of drug action mechanisms and pathophysiological aspects of many diseases\(^{27}\), some authors debate on whether animal researches are valuable predictors of human conditions and pathogenesis, due to interspecies differences and lack of uniform requirements for reporting animal data and comparable results\(^{28}\). Considering the pyramid of medical research, animal experimentation and in vitro studies take their place at the bottom, reflecting basic studies; however, tools of assessment of these studies have emerged in the last decade to improve transparency and accuracy of reports\(^{29}\). One of which, ARRIVE guidelines (Animals in Research: Reporting in Vivo Experiments) creates a checklist of 20 steps to be met during animal experimentation reports\(^{29}\). Although ARRIVE checklist is not mentioned in many animal reports, in the past five years endorsement of this tool amongst journals has risen considerably\(^{30}\), becoming an important source of evaluation. Thus, it was this paper’s intent to grade Animal Experimentation and In Vitro Studies’ Evidence Level, through a personal classification (Table 1), derived from the Oxford Centre for Evidence Based Medicine (CEBM). In addition, apply the ARRIVE checklist to in vivo animal studies referenced in this paper.

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*Modified items from Oxford CEBM

c) Flavonoids

Flavonoids represent one of major polyphenolic groups, which are widely distributed in the plant kingdom and commonly found in vegetables, fruits and teas of the human diet\(^1\). Recent experimental studies and clinical trials conducted with flavonoids, in particular the class of flavonols, have demonstrated a wide variety of physiological effects, including antioxidant, anti-proliferative/antitumor and anti-inflammatory, also correlating some of their action mechanisms to neuroprotective potential. Thus evidencing this class of molecules as an accessible alternative of preventive
therapy or treatment of numerous neurological diseases. Flavonoids can be found in nature as aglycone forms, glycosides or methylated/acylated derivatives. Amongst flavonoids representatives, the best-known molecules are (1) Quercetin, an important aglycone form and a pioneer subject mid flavonoid research; (2) Rutin, main hydrophilic glycoside molecule; and (3) Isoquercitrin (IQ), main lipophilic glycoside, also known as quercetin-3-O-glucoside (Q3G) and Isoquercetin, a nearly identical hydrophilic glycoside molecule; and (3) Isoquercitrin located at the 3 or 4 position of the pyrone ring.

Flavonoids absorption occur predominantly in the small intestine, however it is limited by molecular weight and hydrophilicity. Few studies have been conducted as to elucidate bioavailability and absorption across the blood-brain barrier in human models (Evidence Level 1B), whereas most studies have used in vivo animal models, biological differences and lack of complete physiological understanding of flavonoid’s absorption in the small intestine have limited new findings. Nevertheless, the type of sugar moiety attached to primary aglycone molecule, has been named the major determinant of small intestine absorption, rather than its position in the same molecule.

In food plants, quercetin occurs almost exclusively as glycosides, in which the and the dominant type of glycoside vary amongst foods and is usually located at the 3 or 4 position of the pyrone ring. Onions, kale, broccoli and apples are important sources of glucoside molecules, such as Rutin. IQ is a common naturally occurring glycoside also obtained by enzymatic hydrolysis of rutin with heperedinase, an enzyme produced by specific types of fungi such as Penicillium sp.

Heperedinase has a $\alpha$-l-rhamnosidase selective activity when applied at 58°C for 30 minutes, capable of cleaving the rhamnosidase radical of rutin’s basic structure and leaving the glucoside radical intact, transforming it into IQ. This procedure, generates what is called enzymatic modified IQ or Hydrolysed Rutin (HR), both of which consists of a mixture that includes IQ (69.5%), quercetin (7.5%), rutin and other small metabolites. Studies have shown the superiority of anti-oxidant and anti-proliferative properties of HR when compared solely to quercetin and rutin (Evidence Level 2C).

### III. Neurodegenerative Diseases

Neurodegenerative diseases are a consequence of genetic and environmental factors that are strongly associated with age. These disorders arise from multifactorial conditions that interfere directly with cellular oxidative homeostasis and function. Amongst various pathophysiological factors, increased oxidative stress, mitochondrial dysfunction and abnormal protein dynamics represent a common role in the development of different neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD) and amyotrophic lateral sclerosis (ALS) Also appearing to command numerous neuronal pathways, leading to alterations in neurotransmission and ionic channels, protein aggregation, impaired bioenergetics and even cellular death.

Free radicals are indispensable molecules to cellular function by involvement in many biochemical activities. However, oxidative stress arise from disturbances between pro-oxidant/antioxidant equilibrium. Overproduction of free radicals produce cytotoxicity and genotoxicity by damaging biomolecules, such as proteins, lipids and DNA and leading to arise of various chronic diseases, including in the CNS. In the brain glial and neuronal cells are particularly sensitive to free radicals and actively targeted by ROS. Primary neuroprotective potential of flavonoids rely mainly on their antioxidant effect and leading mechanism of action seems to be reduction of cellular oxidative stress by scavenging and decreasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) in brain tissue (Evidence Level 2C).

Also exhibiting activation of anti-oxidant enzymes (Evidence Level 1B), (Evidence Level 2C), protein disaggregation and diminished production (Evidence Level 2C), decrease of lipid peroxidation (Evidence Level 1B), (Evidence Level 2C), transitional metal chelation (Evidence Level 2C e 4) and anti-inflammation effects (Evidence Level 1B). Although, Ansari et al. (2009) demonstrated in an in vitro study that quercetin showed dual effect on oxidative stress; at lower dosages, antioxidant effects were observed, though in higher dosages, it exhibited a pro-oxidant effect also increasing neuronal dysfunction, it is still clear flavonoids present oxidative-protective effects on various diseases, including those of the CNS.

#### a) Alzheimer’s Disease

Alzheimer’s disease (AD) is a complex neurological disorder clinically characterized by progressive loss of memory and cognition; histopathology demonstrates accumulation of extracellular $\beta$-amyloid plaques (major constituent of senile plaques), intracellular neurofibrillary tangles, tau protein phosphorylation and neurodegeneration of synaptic neurons, especially in the hippocampus. Oxidative stress and neuro-inflammation are also considered hallmarks of AD, mainly responsible for increased neurotoxicity of cognitive-modulating areas. In addition, the decrease in cholinergic neurotransmission has also been implicated in cognitive decline and behavioral changes of AD.

Flavonoids represent an interesting class of phytochemicals and, even before scientific studies, have
been widely used as phytotherapy medicines, like Ginkgo biloba, which includes quercetin and kaempferol67. In 2009, Shi et al. demonstrated quercetin molecule was responsible for high antioxidant activity of this plant extract, corroborating to the hypothesis of flavonoids, in particular flavonols, as possible therapeutic drugs with neuroprotective potential (Evidence Level 2C)68.

A main pathophysiological mechanism of AD is the transformation of β-amyloid peptides into amyloid-beta (Abeta) plaques and the extracellular aggregation of plaques in areas such as the hippocampus67, which appear to be an early phenomenon and is currently used as a diagnostic tool of the disease through PET scan markers (Evidence Level 2A)69. In the last few years, some studies have comprised flavonoid’s neuroprotective potential and investigated anti-amyloidogenic properties. Ansari et al. (2009) demonstrated quercetin’s protective effect under low dosages (5 μM and 10 μM), strongly inhibiting Abeta fibril formation and preventing glutathione oxidation (Evidence Level 2C)60. In 2011, Jimenez-Aliaga evaluated anti-amyloidogenic potential of both quercetin and rutin, demonstrating inhibition of Abeta fibrils formation and disaggregation by both compounds, however, noticing statistical superiority of quercetin’s effects. Also reporting the reduction of ROS production and lipid peroxidation index (Evidence Level 2C)47. In addition, Choi et al. (2014) studied their in vitro activity of a flavonoid panel, including quercetin and rutin, against Abeta-induced toxicity. Results corroborated previous studies showing that flavonoids significantly block Abeta-induced neuronal toxicity (Evidence Level 2C)41.

Liu et al., 2013 investigated in vivo the protective effects of quercetin against Abeta-induced toxicity, on both endothelial cells and neurons, after oral administration of quercetin for a period of 8 days; learning and memory were evaluated by Morris Water Maze test, and cerebral flow was closely monitored. Results showed neurovascular coupling protection, with reduction of oxidative stress and maintenance of neurovascular unit (Evidence Level 1D)62.

Recent in vitro and in vivo studies investigated neuroprotective effects of quercetin on Abeta-induced toxicity models. Results showed quercetin improved cell viability, by diminishing neuronal and endothelial oxidative stress (Evidence Levels 2C, 1D)33,64, and the production of ROS and LDH were decreased, as an increase on superoxide dismutase occurred (Evidence Level 2C)63. Mohabali et al., 2016 demonstrated both Rutin’s and Quercetin’s potential to down regulate inflammation-involved genes in AD (Evidence Level 1D)65. Moreover, Sabogal- Guáqueta et al., performed an in vivo study with quercetin (25mg/kg) i.p. administration, for 3 months, on triple transgenic AD model mice, observing a decrease of extracellular β-amyloid deposition, as well as a reduction of tau phosphorylation, astroglisis and microgliosis in the hippocampus and amygdala (Evidence Level 1D)66.

Isolated, rutin has been less studied in AD over the years. In 2012, Javed et al. conducted the investigation of rutin’s neuroprotective antioxidant effects in an in vivo intracerebroventricular-streptozotocin (ICV-STZ) induced toxicity model. Rutin was pre-administered orally (25mg/kg) for 3 weeks, and results indicated attenuation of STZ-induced inflammation by reducing the expression of cyclooxygenase-2 (COX-2), interleukin-8 (IL-8) and nuclear factor-kB, thus preventing neuro-inflammatory morphological changes in the hippocampus (Evidence Level 1D)67.

In addition, recent studies that comprised rutin’s antioxidant activity on Abeta-induced neurotoxicity showed the decrease of ROS and RNS as the main action mechanism, consequently reducing lipid peroxidation. Interestingly, rutin was also capable of diminishing glutathione levels and dependent enzymes, also downregulating astrocytosis and microgliosis and, therefore, proving to having similar effects to quercetin (Evidence Levels 1D)68-70.

Another hallmark characteristic of AD is the decrease in cholinergic neurotransmission, which has been implicated in cognitive decline, leading to dementia, and behavioral disorders. The increase on cholinergic neurotransmission is an important focus of recent drug therapy and comprises the inhibition of acetylcholinesterase (AchE), acetylcholine’s degrading enzyme. Both quercetin and rutin have been targets of recent studies focusing on AchE inhibition, since it is an important target on Alzheimer’s drug therapy. Quercetin is a strong AchE inhibitor (Evidence Levels 1D, 2B, II)72,73, presenting higher binding strength to active site of the enzyme than some of the drugs in the market, like Donezepil42; also acting in a dose-dependent manner (Evidence Level 3B)32. Rutin also seems to show AchE inhibition properties (Evidence Level 3B)13, however no study has solely involved this compound. There are no studies indexed on PubMed or Scielo involving isoquercitrin’s specific neuroprotective effects in AD. Nevertheless, IQ exhibits important antioxidant activity76 and has been implied as a promising molecule for the treatment of several pathologies, especially cancer77.

b) Parkinson’s Disease

Parkinson’s disease (PD) is a neurodegenerative movement disorder mainly characterized by progressive loss of dopaminergic neurons within nigrostriatal pathway, affecting substantia nigra area, and associated with microglial-mediated neuro-inflammation22. Pathogenic aspects of PD involve mitochondrial dysfunction, changes in micro-RNA and α-synuclein levels13, a major constituent of Lewy bodies and a hallmark of PD28. Oxidative stress has been

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associated as a risk factor for dopamine cellular degeneration of PD\textsuperscript{79}, and mitochondrial dysfunction plays an important role on energetic balance as well as regulating oxidative and apoptotic pathways\textsuperscript{38}.

Quercetin has been widely investigated for its antioxidant effects; however, specific PD model investigations are scarce. On chronic rotenone (ROT)-induced parkinsonian models quercetin (25-75mg/kg i.p.) showed reduced loss of ROT-induced dopaminergic neurons, also decreasing glutathione levels and increasing anti-oxidant enzymes (catalase and superoxide dismutase) (Evidence Level 2B)\textsuperscript{80}. In 2015, Denny Joseph et al., also investigated on ROT-induced models the beneficial effects of treatment association between fish oil and quercetin. Results corroborated previous studies demonstrating significant behavioral change as well as attenuation of oxidative stress and mitochondrial dysfunction indicators (Evidence Level 1D)\textsuperscript{81}.

Other studies using methyl-4-phenylpyridinium ion (MPP(+)), a parkinsonian toxin that provokes degeneration of dopaminergic neurons\textsuperscript{82}, and 6-hydroxydopamine (6-OHDA), a selective dopaminergic neurotoxin\textsuperscript{83}. Also demonstrated quercetin’s neuroprotective potential by reducing apoptotic neuronal death, through modulation of pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) genes, and decreasing oxidative stress and neuro-inflammation (IL-1, TNF-\alpha and COX-2) on microglial cells (Evidence Levels 2C, 2C, 1D, 1D)\textsuperscript{82-88}. Although these results are consistent with literary review appointing quercetin as an antioxidant molecule, some studies have shown a paradoxical effect of this compound when used in high dosages (Evidence Level 2C)\textsuperscript{89}.

In addition, in 2015, Ahn et al. investigated quercetin’s specific effect on \alpha-synuclein expression. During the experiment, PC12 cells were pre-treated with quercetin and results showed quercetin presents neuroprotective effects affecting various mechanisms such as apoptosis and oxidative stress; however, quercetin treatment increased \alpha-synuclein levels, and although cell viability and survival were unaltered with the up-expression, this data suggests quercetin’s effects on PD is still not entirely understood (Evidence Level 2C)\textsuperscript{90}.

During the course of 2014 to 2016, Magalingam et al., produced a series of three articles investigating Rutin and Isoquercitrin on 6-OHDA PD-induced models. Both rutin and IQ demonstrated antioxidant effects by reducing lipid peroxidation and increasing anti-oxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) (Evidence Level 2C)\textsuperscript{86-88}. Cytoprotective activity of IQ occurred in a dose-dependent manner. Furthermore, Rutin showed upregulation of the TH gene, an important factor in dopamine biosynthesis; as well as modulation of apoptotic pathways by reducing Park2, Park5, Park7, Caspase 3 and Caspase 7 genes (Evidence Level 2C)\textsuperscript{86}.

c) Huntington’s Disease

Huntington’s disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder clinically characterized by motor, cognitive and behavioral impairment, also presenting high morbidity and mortality rates\textsuperscript{89}. Incidence is higher at European countries and mean age of symptoms onset occurs around 40 years old \textsuperscript{90}. HD is cause by an expanded CAG trinucleotide repeat in the HTT gene, responsible for encoding the protein huntingtin. The mutation lead to the production of an abnormal protein with long polyglutamine sequences that confers toxic properties and predisposes protein fragmentation, which can result in neuronal death\textsuperscript{91}.

Quercetin is the only major flavonol whose neuroprotective effect has been associated to Huntington’s disease treatment potential. In this review, we found no articles investigating rutin or isoquercitrin effects on HD models. In 2013, Sandhir et al., evaluated oral supplementation of quercetin (25mg/kg) on 3-nitropropionic acid-induced (3-NP) Huntington’s disease animal model. Posterior analysis was conducted on mitochondrial biogenetics, oxidative stress, neurobiological behaviors and histopathological assays. It was proven quercetin exhibits protective effects by attenuating mitochondrial oxidative stress (reduced lipid peroxidation and mitochondrial swelling), as well as increasing motor skills and antioxidant elements (Evidence Level 2B)\textsuperscript{92}. Additionally, in 2014, quercetin was once again tested on 3-NP-induced HD models, confirming previous results of antioxidant properties and motor coordination increase, along with display of behavioral changes through lessening of anxiety and isolation; also reducing neuro-inflammatory responses with an increase of astrocyte numbers in core lesions and decreased microglial proliferation (Evidence Level 1D)\textsuperscript{93,94}.
Flavonoids have been widely investigated in the past decades and have shown a wide variety of physiological effects, determining a therapeutic potential on innumerable diseases, including neurological pathologies. Their neuroprotective effects are mostly related to anti-oxidant and anti-inflammatory properties; however, specific mechanisms have been reached on in vitro and in vivo animal models of neurodegenerative diseases. It is quite difficult to assess on whether animal experimentation is most likely to predict human outcomes and toxicity, nonetheless, it is a vital part of scientific research and discovery. Evidence-based medicine analyses such studies in order to foresee favorable outcomes, and although most studies conducted with flavonols are in vitro and animal models of experimentation (Evidence Level 1D/2B and 2C), ARRIVE guidelines offer a tool of assessment, in order to improve transparency and accuracy of these reports. Our findings on the subject suggest in vitro studies are still the majority of literature references, yet in vivo animal experimentation references seem to be well-constructed(Table 2) and able to provide key results, leading to the possibility of human clinical trials. Despite the lack of human trials with Quercetin, Rutin and Isoquercitrin, other flavonoids have been tested and results show neurological features, providing a glimpse of the therapeutic potential of these compounds. We also suggest Isoquercitrin as a viable option to future experiments, due to its superiority of anti-oxidant and anti-proliferative properties.

### Table 2: ARRIVE Checklist evaluation of in vivo Animal Studies referenced

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Flavonoid Tested</th>
<th>ARRIVE Checklist Items Met</th>
<th>ARRIVE Checklist Items Not-Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. 62</td>
<td>2013</td>
<td>Quercetin</td>
<td>1-9, 10a, 11b, 12-20</td>
<td>10b, 11a</td>
</tr>
<tr>
<td>Hayakawa et al. 54</td>
<td>2015</td>
<td>Quercetin</td>
<td>1,2,3a, 4-9, 11-13, 15-20</td>
<td>3b, 10, 14</td>
</tr>
<tr>
<td>Sabogal-Guadueta et al. 56</td>
<td>2015</td>
<td>Quercetin</td>
<td>1,2,3a, 4-8,11b, 12,13, 16-20</td>
<td>3b, 8a, 10, 11a, 14,15</td>
</tr>
<tr>
<td>Javed et al. 67</td>
<td>2012</td>
<td>Rutin</td>
<td>1, 2, 3a, 4-9, 10a, 12, 13, 15-20</td>
<td>3b, 10b, 10c, 11, 14</td>
</tr>
<tr>
<td>Choi et al. 58</td>
<td>2015</td>
<td>Rutin</td>
<td>1-9, 10a, 11-20</td>
<td>10b, 10c</td>
</tr>
<tr>
<td>Xu et al. 69</td>
<td>2014</td>
<td>Rutin</td>
<td>1, 2, 3a, 4-9, 10a, 11-13, 15-20</td>
<td>3b, 10b, 10c, 14</td>
</tr>
<tr>
<td>Moghbelinejad et al. 70</td>
<td>2014</td>
<td>Rutin</td>
<td>1,2,3a, 4, 5, 6a, 6c, 7, 8b, 9, 12, 13, 15-20</td>
<td>3b, 6b, 8a, 10, 11, 14</td>
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<td>Abdalla et al. 72</td>
<td>2014</td>
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<td>Karuppagounder et al. 80</td>
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<td>Zhang et al. 83</td>
<td>2011</td>
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<td>2013</td>
<td>Quercetin</td>
<td>1-20</td>
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<tr>
<td>Jain et al. 86</td>
<td>2014</td>
<td>Quercetin</td>
<td>1, 2, 3a, 4-20</td>
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<tr>
<td>Chakraborty et al. 84</td>
<td>2014</td>
<td>Quercetin</td>
<td>1-5, 6a, 6b, 7-10, 12-14, 16-20</td>
<td>6c, 11, 15</td>
</tr>
</tbody>
</table>

### IV. Conclusion

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Cerebellar Dysplastic Gangliocytoma as the First Presentation of Cowden Syndrome

By Abdulrhman Alnasser, Roaa Amer & Eman Bakhsh

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Abstract- Cowden syndrome is a rare autosomal-dominant disease characterized by multisystem hamartomas usually affecting the skin, thyroid gland, breast, and gastrointestinal tract; these hamartomas tend to undergo malignant transformation in various tissues. We describe a 32-year-old woman who presented with a progressive headache, neck pain, nausea, vomiting, transient loss of vision, dizziness, and unsteady gait during the previous 2 months; she had one episode of a seizure and a previous history of an ovarian cyst manifesting as abnormal menses. Brain magnetic resonance imaging (MRI) revealed a left cerebellar mass with features suggestive of dysplastic gangliocytoma with obstructive hydrocephalus in addition to multiple meningiomas. Imaging features raised the suspicion of Cowden syndrome (CS). Thus, the patient underwent suboccipital craniotomy for resection of the left cerebellar mass; pathological and immunohistochemical examination confirmed the diagnosis of CS. Most cases found in the literature reported delayed diagnoses of this condition; however, our patient’s peculiar MRI features facilitated early diagnosis and likely prevented or delayed possible complications. This case highlights the clinical manifestations and diagnostic criteria of CS even in the absence of mucocutaneous manifestations.

GJMR-A Classification : NLMC Code: WL 140
Cerebellar Dysplastic Gangliocytoma as the First Presentation of Cowden Syndrome

Abdulrhman Alnasser α, Roaa Amer α & Eman Bakhsh α

Abstract: Cowden syndrome is a rare autosomal-dominant disease characterized by multisystem hamartomas usually affecting the skin, thyroid gland, breast, and gastrointestinal tract; these hamartomas tend to undergo malignant transformation in various tissues. We describe a 32-year-old woman who presented with a progressive headache, neck pain, nausea, vomiting, transient loss of vision, dizziness, and unsteady gait during the previous 2 months; she had one episode of a seizure and a previous history of an ovarian cyst manifesting as abnormal menses. Brain magnetic resonance imaging (MRI) revealed a left cerebellar mass with features suggestive of dysplastic gangliocytoma with obstructive hydrocephalus in addition to multiple meningiomas. Imaging features raised the suspicion of Cowden syndrome (CS). Thus, the patient underwent suboccipital craniotomy for resection of the left cerebellar mass; pathological and immunohistochemical examination confirmed the diagnosis of CS. Most cases found in the literature reported delayed possible complications. This case highlights the clinical manifestations and diagnostic criteria of CS even in the absence of mucocutaneous manifestations.

I. Introduction

Cowden syndrome (CS), which was first described by Lloyd and Dennis in 1963 and is also known as PTEN hamartoma tumor syndrome, is a rare autosomal-dominant disease characterized by multisystem hamartomas usually affecting the skin, thyroid gland, breast, and gastrointestinal tract [1]. Germline mutations in the PTEN gene are thought to constitute the etiology of this syndrome [2]. Although hamartomas are the most common manifestation of this disease, CS has also been linked to many types of cancers such as those of the breast, thyroid, and uterus [2]. Other less common types of cancer include colorectal, kidney, and skin cancers [2,3]. In rare cases, benign brain tumors can occur; these have been linked to a small percentage of individuals with intellectual disabilities [2]. In this study, we describe a 32-year-old woman with an early manifestation of CS; our particular case highlights the clinical manifestations and diagnostic criteria of CS even in the absence of mucocutaneous manifestations.

II. Case Report

A 32-year-old Saudi woman presented to the neurology clinic with a progressive headache, neck pain, nausea, vomiting, transient visual loss, dizziness, and an unsteady gait for the past 2 months. She had also experienced one episode of a seizure and had a history of an ovarian cyst manifesting as abnormal menses. The patient had no notable family history of malignancy; she had undergone resection of a mass that was diagnosed as a lipoma in her lower back two years prior. Physical examination revealed conjunctival pallor, diffuse thyroid goiter, pectus excavatum, and a scar in her left lower back due to the aforementioned resection. No cutaneous or mucosal abnormalities were noted.

Initial blood work was normal except for a hemoglobin level of 9g/dL and a low mean corpuscular volume (70 fL). Thyroid function tests, erythrocyte sedimentation rate, C-reactive protein, and lactate dehydrogenase were all normal. Magnetic resonance imaging (MRI) of the brain revealed a left cerebellar expansile mass with widened cerebellar folia that caused a compression effect over the fourth ventricle, with supratentorial tri-ventricular hydrocephalus consistent with dysplastic gangliocytoma (Figure 1A and 1B). Furthermore, multiple dural-based intensely enhancing masses were noted in the right temporal lobe and the retroclival regions; this was consistent with multiple meningiomas (Figure 2). The patient underwent suboccipital craniotomy for resection of the left cerebellar lesion. Immunohistochemistry was positive for synaptophysin, and molecular genetic testing confirmed the presence of a PTEN 10q23.31 mutation. Full sequencing of PTEN revealed a heterozygous G to T mutation on exon 7. The final diagnosis was CS.

Next, a full screen for other possible manifestations of her disease was performed; this revealed hypervascular multinodular goiter on thyroid ultrasonography and a thinning of the endometrial stripe (<2mm) on pelvic ultrasonography. Breast ultrasonography revealed evidence of fibrocystic disease, and breast MRI was highly suggestive of breast imaging-reporting and data system (BI-RADS) IV. A true cut biopsy from both breasts confirmed the diagnosis of sclerosing intraductal papilloma, while a colonoscopy revealed the presence of extensive hyperplastic rectal polyps. Further evaluation of the...
gastrointestinal tract was performed using a barium study, which showed nodular thickening of the mucosal fold in the terminal ileum. Lastly, prophylactic mastectomy and rectal polyectomy were discussed and recommended to the patient, and the importance of follow-up and continuous surveillance was emphasized. The patient is currently performing well with no neurological symptoms.

III. Discussion

CS is a rare autosomal dominant disease that is mainly characterized by hyperplastic hamartomas and tumoral lesions affecting multiple organs [1,4]. Furthermore, this disease can predispose patients to multiple cancers; it is usually diagnosed during the third decade and is predominant in women [5]. Ectodermal, endodermal, and mesodermal alteration is a known feature of this syndrome, which reflects the range of affected organs [5]. The most commonly affected organs in order of frequency are the skin, mucus membranes, breast, bone, gastrointestinal tract, thyroid, genitourinary system, and central nervous system (CNS) [5,6,7].

Numerous CNS tumors have been linked to the same gene mutation found in CS, most of which were discovered in asymptomatic patients [8]; CNS manifestations are only observed in one-fifth of patients with CS [5,8]. A possible link between PTEN mutations and developmental delay or mental retardation has been reported (reviewed in [8]). Another CNS manifestation is macrocephaly, which is observed in 80–100% of patients with PTEN mutations [8]. Autism spectrum disorders have also been linked to CS [8]; furthermore, dysplastic gangliocytoma of the cerebellum, also known as Lhermitte-Duclos disease (LDD), is considered a pathognomonic feature of CNS manifestations of CS [7,8].

LDD is a rare, non-malignant, slow growing hamartoma that is commonly asymptomatic or exhibits relatively subtle cerebellar signs. If sufficiently large, however, symptoms may include headaches, visual problems, cerebellar ataxia, and signs of increased intracranial pressure [8]; these symptoms were apparent in our patient. LDDIs usually diagnosed in the second or third decade of life; diagnosis of this disease in adulthood has been linked to CS more so than in children [8,10]. The microscopic appearance of LDD usually manifests as disarrangement of the laminar cellular architecture of the cerebellum. Additionally, invasion of the inner granular layer of the cerebellum, loss of the middle Purkinje layer, and thickening of the outermost layer are observed. Radiographic features of LDD usually exhibit abnormalities in the tissues involving the cerebellar cortex, and usually only on one hemisphere (rarely both), with involvement of the vermis occasionally observed. Computed tomography may only show a nonspecific hypoattenuating cerebellar mass, and calcification may also be rarely observed. On MRI, the lesion is usually confined to one cerebellar hemisphere showing widened cerebellar folia with a striated tigroid appearance; enhancement of such lesions is rare.

In the present case, the clinical presentation of our patient together with MRI findings of a left cerebellar mass with obstructive hydrocephalus mandated surgical resection; this resection was complete, and no recurrence was observed on MRI during the 3-year follow-up period. The retroclival and right temporal meningiomas did not undergo surgical intervention since the patient was asymptomatic with no mass effect noted over the adjacent intracranial structures.

Mucocutaneous manifestations are considered the most common signs of CS, and almost 100% of patients will have at least one type of manifestation. These may include facial papules (trichilemmomas), acral keratoses, papillomatous papules, mucosal papillomas, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma [1,5]. Moreover, these manifestations are essential for the diagnosis of CS; however, they have very little malignant potential [1,3,8]. Despite the high prevalence of these manifestations in CS, our patient did not show any such mucocutaneous lesions.

CS is commonly associated with breast cancer; the lifetime risk of which is approximately 77% in patients with CS [8]. Furthermore, benign breast lesions are known to be a key diagnostic criterion for CS [2]; fibrocystic disease is found in 75% of all female patients with CS [8]. Moreover, fibroadenomas and intraductal papillomas are also associated with CS [8]. Our patient was unique in that she had both fibrocystic disease and intraductal papilloma simultaneously. Moreover, the most frequent genitourinary tract features in women with CS are ovarian cysts, functional menstrual irregularities, leiomyoma, and endometrial cancer [5]. This was true in our patient, who reported irregular menstrual cycles in the previous two months.

The gastrointestinal tract is commonly involved in patients with CS, with a cumulative cancer risk in the colon, rectum, and (rarely) small intestines of 16% [8]; these lesions most commonly manifest as hamartomatous polyps [5,8]. However, this was not the case for our patient, who had extensive hyperplastic rectal polyposis. Although most polyps do not carry a malignant potential, 13% of patients with CS who underwent colonoscopy were found to have colorectal cancer in one study [8]. Moreover, our patient showed nodular thickening of the mucosal fold in the terminal ileum upon undergoing a barium study, suggesting the presence of small bowel polyps.

Other CS manifestations include diseases of the bone and thyroid [1,2,5]. Skeletal manifestations are observed in 37% of all patients with CS [5]; these
include macrocephaly, polydactyly, syndactyly, bone cysts, and kyphoscoliosis [5]. Thyroid diseases include multinodular goiter, thyroiditis, and thyroid cancer [8]. Macrocephaly and bilateral thyroid lesions were noted at the initial presentation of our patient.

A provisional diagnosis of CS was made mainly based on the presence of LDD, thyroid disease, fibrocystic disease, gastrointestinal hamartomas, and lipoma [2,8]. Our patient’s symptoms fulfilled the clinical criteria of the International Cowden Consortium [9], according to which one major criterion (any of: breast carcinoma, thyroid carcinoma, macrocephaly, and endometrial carcinoma) and three minor criteria (any three of: noncancerous thyroid lesions, IQ ≤75, gastrointestinal hamartomas, lipomas, breast fibrocystic disease, uterine fibroids, fibromas, and genitourinary tumors or malformations) represent a diagnosis of CS. Most patients with CS have a germline mutation in the tumor suppressor gene PTEN. Loss of function of PTEN contributes to cellular transformation, increasing the risk of cancer development, premature death, and resistance to chemotherapy and radiation. The presence of a PTEN 10q23.31 mutation was confirmed in our patient [9].

Management of patients with CS necessitates a multidisciplinary treatment and surveillance plan [2]. Full blood count, urinalysis, thyroid function test, and mammography are baseline studies required for CS diagnosis, and should be repeated as often as clinically necessary. Frequent and thorough physical examinations are mandatory to detect any complications of this syndrome. Patient education regarding the possible signs and symptoms of cancer is crucial, as is emphasizing the importance of lifelong follow-up and genetic counseling as requires [3].

IV. Conclusion

Most patients with CS who were reported in the literature had delayed diagnoses. Although our patient did not have any mucocutaneous manifestations, which is the most common presentation of CS, the presence of left cerebellar LDD and multiple meningiomas on imaging were strong indicators of CS. This facilitated early diagnosis and may have served to prevent or delay any future possible complications.

References Références Referencias

Figure 1A: Axial T2-weighted magnetic resonance imaging of the brain showing the left cerebellar mass with widened cerebellar folia, a striated pattern, and preserved cortex. Note the retroclivaldural-based isointense mass on the right side representing retroclival meningioma.
Figure 1B: Post-contrast axial spoiled gradient echo images of the brain showing no enhancement in the left cerebellar mass. Note the intensely enhancing retroclival lesions representing meningioma.
Figure 1: Post-contrast axial spoiled gradient echo images of the brain showing adural-based, intensely enhancing extra-axial mass in the right temporal region representing meningioma. Note the dilated lateral ventricles representing hydrocephalus caused by the previously described left cerebellar mass.
The Benefits of Neuroids/Neuropeptides in Combating Cerebrovascular, Neurological and Ocular Diseases

By M Ishaq Khan & J.I. Khan

Walden University

Abstract- Neuroids and neuropeptides (ND/NPs) are drugs with promising efficacy in cerebrovascular diseases. In this article the benefits and mechanisms of action of ND/NPs for stroke are reviewed in light of the pathogenesis of stroke. The primary mechanism is that ND/NPs help in the synthesis of acetylcholine and betaine. These, in turn, work to help in the formation of nerve cell membrane phospholipids and attenuate the production of free radicals. This is important in stroke because brain damage after stroke is associated with excess production of free radicals. Furthermore, ND/NPs may stimulate the activity of glutathione reductase and have the ability to promote learning and improve cognitive impairment. Pharmacokinetics suggests that ND/NPs are well absorbed, with a higher degree of bioavailability when administered orally. A dose of 500 mg to 2,000 mg per day in slow releasing form is an effective regimen based on clinical trials, and is safe for use in elderly population and pediatrics.

Keywords: betaine, choline, citicoline, neurological dysfunction, neuroids, neuroprptides, phosphatidylcholine.

GJMR-A Classification : NLMC Code: WL 358.5, WL 302, WW 410

Strictly as per the compliance and regulations of:
The Benefits of Neuroids/Neuropeptides in Combating Cerebrovascular, Neurological and Ocular Diseases

M Ishaq Khan & J.I. Khan

Abstract- Neuroids and neuropeptides (ND/NPs) are drugs with promising efficacy in cerebrovascular diseases. In this article the benefits and mechanisms of action of ND/NPs for stroke are reviewed in light of the pathogenesis of stroke. The primary mechanism is that ND/NPs help in the synthesis of acetylcholine and betaine. These, in turn, work to help in the formation of nerve cell membrane phospholipids and attenuate the production of free radicals. This is important in stroke because brain damage after stroke is associated with excess production of free radicals. Furthermore, ND/NPs may stimulate the activity of glutathione reductase and have the ability to promote learning and improve cognitive impairment. Pharmacokinetics suggests that ND/NPs are well absorbed, with a higher degree of bioavailability when administered orally. A dose of 500 mg to 2,000 mg per day in slow releasing form is an effective regimen based on clinical trials, and is safe for use in elderly population and pediatrics.

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I. Introduction

Neuroids and neuropeptides (ND/NPs) are brain chemicals and small proteinaceous substances with wide-ranging efficacy for cerebrovascular diseases associated with trauma, intoxication, drug interactions, and aging (1).

Biochemically, ND/NPs work together in the synthesis of cell membrane compounds (e.g., phosphatidylcholine, Betaine) that generate phospholipids (2). ND/NPs also attenuate the production of free radicals, promote learning, and improve cognitive impairment in brain atrophy (3). The purpose of this article is to present a brief review of the mechanisms and benefits of ND/NPs for neurological disease, especially in preventing brain injury after stroke. First, we present a brief pathogenesis of stroke, including information on diagnosis and treatment, to situate the following text on ND/NPs.

II. Oxidative Stress in Stroke

Stroke is associated with oxidative stress, through an excessive generation of reactive oxygen species (O2S) by mitochondria(4). Excessive O2S generation is the main cause of oxidative stress. Enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NADPase) have recently been recognized and studied as important producers of O2S in brain tissues after stroke. NADPase causes neuronal inflammation and necrosis and plays an important role in brain injury after stroke (5). The enzyme is classically considered as a key part of the electron transport chain in the plasma membrane. In the process of oxidation, it produces O2S by reducing one electron in molecular oxygen and turning out a series of secondary products (such as ozone, singlet oxygen, hydrogen peroxide, hydroxyl radical, superoxide, and sodium hypochlorite) (5). These molecules, also known as free radicals, are the main source of oxidative stress disseminated in the cerebral tissues and vasculature. NADPase moieties are also found in the non-phagocytic cells and sustain low levels of activity even without extracellular stimulation. The enzymes persistently serve as electron donors to produce O2S (6).

Several clinical pharmaceutical studies have established that NADPase inhibitors improve brain injury and improve neurological outcome after stroke. NADPase enzymes contribute to the progression of brain injury after ischemic stroke. NADPase plays a role in nerve growth factor (NGF) induced neuronal differentiation of PC12 cells, while O2S produced by NADPase help to regulate development of neuronal cells (7). However, excessive O2S production after stroke can lead to brain injury. Therefore, prevention of post-stroke brain injury via NADPase inhibitors or via compounds that protect against damage from O2S is important.

III. Diagnosis of Stroke

A stroke patient may present with any of a range of symptoms, including the following:

- An abrupt onset of weakness/numbness in the face, arms, or legs, especially on one side of the body.
- Inability to speak properly.
- Unexpected difficulty in seeing in one or both eyes.
- Problems in walking, giddiness, poor coordination.
- Severe headache with no known cause.
Diagnosis can begin with auscultation of the carotids for reduced blood flow due to any obstruction, such as plaque formation. Brain computed tomography (CT) may show bleeding in the brain or ischemic changes to the nerve cells from stroke. The test can also show other brain conditions that may be causing stroke symptoms. Magnetic resonance imaging (MRI) can detect changes in brain tissue and damage to brain cells from a stroke. This also helps in the detection of the site of a blood clot restricting the flow of blood to the brain. Carotid angiography involves getting pictures of the inside of carotids through sound waves by injecting contrast media that highlight any narrowing/obstruction of the carotids, which may help in grading the type and intensity of carotid obstructions. Electrocardiogram (EKG) can exclude cardiac arrhythmia (fibrillation/flutter, prolongation of the PR interval).

In addition to diagnostic tests, risk factors should also be assessed at presentation. Blood tests are also important. Abnormal platelet levels may promote recurrent stroke because of the recurrent bleeding disorder. Blood tests to measure how long it takes for blood to clot (BT/CT) can identify patients at risk for recurrence, as well. Finally, lipid profiles can identify recurrence risk, because raised blood cholesterol and lipoproteins are significant risk factors for stroke. Several triggering factors act either directly (head injury, head and neck surgeries) to cause episode of stroke, or indirectly via high blood pressure, uncontrolled diabetes, dyslipidemia, metabolic disorders [Fig1].

Figure 1: Direct and Indirect triggering factors

IV. ND/NP MECHANISMS OF ACTION

For several years ND/NPs have been known for their promising action in biomedical sciences. ND/NPs include choline, ribose, pyrophosphate, cytosine, and peptides (8). These are essential intermediary ingredients in the synthesis of cell membrane phospholipids (Phosphatidycholines), a primary neurotransmitter (9). The latter are integral cell constituents and have a high yield rate, which entails a constant production of these constituents to guarantee the satisfactory function of cell membranes (10). As shown in Figure 1, ND/NPs function by generating phospholipids, including cytidine, choline, and neuropeptides. These promote synthesis and repair of nerve cell membranes, as well as removal of fatty acids and other degradation products at the site of nerve damage. The result is improved nerve function, including mood and memory improvements.

In the treatment of ischemia for prevention of brain stroke, ND/NPs delays the deposition of free fatty acids and formation of free radicals at the site of ischemia, thus preventing the start of proinflammatory cascades of episodes(11). This occurs through breakdown of cerebral phospholipids, exerting a protective effect upon the cell membrane ATPase and enzymes (succinyl dehydrogenase and citrate synthetase) drawn in brain energy metabolism.

In the brain, ND/NPs are the most varied class of signaling molecules involved in several physiological functions. As of today, over 70 associated genes have been identified (12). These are traced to decisive bioactive neuropeptides working in the nervous system. ND/NPs excite chemical signals, which in turn induce neurosecretion of peptide hormones in the endocrine system through sensitive nerve endings in the hypothalamus (13). ND/NPs are widely available as approved drugs for the treatment of neurological disorders. On administration, these drugs are hydrolyzed in the intestinal tract and in circulation, form useful neurogenic products such as cytidine, choline, and others (14).
Doses as high as 500 mg–2000 mg slowly administered per day have been effectively absorbed from the gastrointestinal tract, metabolites excreted through urine, respiratory tract, and feces, with minimal excretion through feces (15).

**Figure 2:** Life Cycle of Neuroids and Neuropeptides (ND/NPs)

*CNS=central nervous system (including brain)*

**Benefits for Neurological Disease**

ND/NPs have been revealed to work as a dopaminergic receptor agonist, inducing monoamines, serotonin, nor epinephrine, and glutamate/GABA at muscarinic site (16). Thereby, ND/NPs have been found to endorse learning and advance cognitive impairment in Parkinson’s and Alzheimer’s diseases (17). In addition, these neuroids lessen the severity of mental and motor insufficiency related to head injuries and support eye and mental health by improving phospholipid metabolism (18). ND/NPs help in the development of reduced axonal flow of dopamine. Owing to its ability to repair neuronal membranes and its ability to augment central nervous system dopamine levels, ND/NPs have been considered for the treatment of neuronal disrepair caused by infectious agents (19).

Neurological issues in the face and extremities are also of interest, because ND/NPs can be of benefit in myasthenia graves, ocular/extraocular paresis (meosis, proptosis), facial nerves palsy, diabetes, polyneuropathies, attention deficit/hyperactivity disorder (ADHD) and restless leg syndrome. Neurosecretion of acetylcholine by the ND/NPs causes helpful stimulation of small muscles in the eyes. Secretion of neurotransmitters in individuals treated with ND/NPs leads to variable degrees of improvement in muscle nerve function (20). With follow up, the resultant improvement in muscle contraction from ND/NPs treatment was been more encouraging than placebo (21). As such, ND/NPs may be used to increase acetylcholine levels and improve muscle contraction or movement (22). Thus, ND/NPs causes hormone increases (acetylcholine and derivatives) by acting to inhibit cholinesterase, the enzyme that destroys acetylcholine, at the nerve–muscle junctions (23).

ND/NPs have been found to have a levodopa-sparing effect and an ability to increase dopamine synthesis. Higher doses of ND/NPs (.5 g–1g) for 15 days have thus shown favorable effect on eye health, in particular for amblyopia and glaucoma (24). Glaucoma is considered a neurodegenerative disease, further supporting the role of ND/NPs in its treatment and prevention.

**V. Conclusion**

ND/NPs are unique compounds possessing wide-ranging benefits in diseases associated with neurological disorders, cerebrovascular disorders, and ocular disorders (25). They uphold neural health and good cognitive function while suppressing the damaging effects of free radicals and boosting antioxidant mechanisms in the body. In addition, ND/NPs can advance anti-inflammatory activities and energize neurotransmitter related activities (26). Therefore, these compounds are of continued interest both clinically and for research. In addition to preventing brain damage after stroke, ND/NPs have promising applications for a range of neurological disorders.


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*Language:* The language of publication is UK English. Authors, for whom English is a second language, must have their manuscript efficiently edited by an English-speaking person before submission to make sure that, the English is of high excellence. It is preferable, that manuscripts should be professionally edited.

Standard Usage, Abbreviations, and Units: Spelling and hyphenation should be conventional to The Concise Oxford English Dictionary. Statistics and measurements should at all times be given in figures, e.g. 16 min, except for when the number begins a sentence. When the number does not refer to a unit of measurement it should be spelt in full unless, it is 160 or greater.

Abbreviations supposed to be used carefully. The abbreviated name or expression is supposed to be cited in full at first usage, followed by the conventional abbreviation in parentheses.

Metric SI units are supposed to generally be used excluding where they conflict with current practice or are confusing. For illustration, 1.4 l rather than 1.4 × 10^-3 m³, or 4 mm somewhat than 4 × 10^-3 m. Chemical formula and solutions must identify the form used, e.g. anhydrous or hydrated, and the concentration must be in clearly defined units. Common species names should be followed by underlines at the first mention. For following use the generic name should be constricted to a single letter, if it is clear.

**Structure**

All manuscripts submitted to Global Journals Inc. (US), ought to include:

*Title:* The title page must carry an instructive 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) wherever the work was carried out. The full postal address in addition with the e-mail address of related author must be given. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining and indexing.

*Abstract, used in Original Papers and Reviews:* Optimizing Abstract for Search Engines

Many researchers searching for information online will use search engines such as Google, Yahoo or similar. By optimizing your paper for search engines, you will amplify the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in a further work. Global Journals Inc. (US) have compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

*Key Words*  

A major linchpin in research work for the writing research paper is the keyword search, which one will employ to find both library and Internet resources.

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

Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art. A few tips for deciding as strategically as possible about keyword search:
One should start brainstorming lists of possible keywords before even begin 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 research paper?" Then consider synonyms for the important words.

It may take the discovery of only one relevant 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.

One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher’s skills are bound to improve with experience and time.

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

Acknowledgements: Please make these as concise as possible.

References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author’s name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

The Editorial Board and Global Journals Inc. (US) recommend that, citation of online-published papers and other material should be done via a DOI (digital object identifier). If an author cites anything, which does not have a DOI, they run the risk of the cited material not being noticeable.

The Editorial Board and Global Journals Inc. (US) recommend the use of a tool such as Reference Manager for reference management and formatting.

Tables, Figures and Figure Legends

Tables: Tables should be few in number, 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. Vertical lines should not be used.

Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.

Preparation of Electronic Figures for Publication

Even though low quality images are sufficient for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit (or e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings) in relation to the imitation size. Please give the data for figures in black and white or submit a Color Work Agreement Form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution (at final image size) ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs) : >350 dpi; figures containing both halftone and line images: >650 dpi.
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Figure Legends: Self-explanatory legends of all figures should be incorporated separately under the heading 'Legends to Figures'. In the full-text online edition of the journal, figure legends may possibly be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should notify the reader, about the key aspects of the figure.

6. AFTER ACCEPTANCE

Upon approval of a paper for publication, the manuscript will be forwarded to the dean, who is responsible for the publication of the Global Journals Inc. (US).

6.1 Proof Corrections

The corresponding author will receive an e-mail alert containing a link to a website or will be attached. A working e-mail address must therefore be provided for the related author.

Acrobat Reader will be required in order to read this file. This software can be downloaded

(Free of charge) from the following website:

www.adobe.com/products/acrobat/readstep2.html. This will facilitate the file to be opened, read on screen, and printed out in order for any corrections to be added. Further instructions will be sent with the proof.

Proofs must be returned to the dean at dean@globaljournals.org within three days of receipt.

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**TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:**

1. **Choosing the topic:** In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be “Yes” then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

2. **Evaluators are human:** First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

3. **Think Like Evaluators:** If you are in a confusion or getting demotivated that your paper will be accepted by evaluators or not, then think and try to evaluate your paper like an Evaluator. Try to understand that what an evaluator wants in your research paper and automatically you will have your answer.

4. **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.

5. **Ask your Guides:** If you are having any difficulty in your research, then do not hesitate to share your difficulty to your guide (if you have any). They will surely help you out and resolve your doubts. If you can’t clarify what exactly you require for your work then ask the supervisor to help you with the alternative. He might also provide you the list of essential readings.

6. **Use of computer is recommended:** As you are doing research in the field of Computer Science, then this point is quite obvious.

7. **Use right software:** Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

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9. **Use and get big pictures:** Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

10. **Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

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12. **Make all efforts**: Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

13. **Have backups**: When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

14. **Produce good diagrams of your own**: Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

15. **Use of direct quotes**: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

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

17. **Never use online paper**: If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

18. **Pick a good study spot**: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. **Know what you know**: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. **Use good quality grammar**: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straightforward. put together a neat summary.

21. **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 to your topic. You may also maintain your arguments with records.

22. **Never start in last minute**: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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

24. **Never copy others’ work**: Never copy others’ work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. **Take proper rest and food**: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. **Go for seminars**: Attend seminars if the topic is relevant to your research area. Utilize all your resources.
27. **Refresh your mind after intervals**: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. **Make colleagues**: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. **Think technically**: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. **Think and then print**: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. **Adding unnecessary information**: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. **Never oversimplify everything**: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. **Report concluded results**: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. **After conclusion**: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to 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 in 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 criterion for grading the final paper by peer-reviewers.

**Final Points:**

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of 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 the 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 evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

- Use standard writing style including articles ("a", "the," etc.)
- Keep on paying attention on the research topic of the paper
- Use paragraphs to split each significant point (excluding for the abstract)
- Align the primary line of each section
- Present your points in sound order
- Use present tense to report well accepted
- Use past tense to describe specific results
- Shun familiar wording, don’t address the reviewer directly, and don’t use slang, slang language, or superlatives
- Shun use of extra pictures - include only those figures essential to presenting results

**Title Page:**

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

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript—must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing 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 approach 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. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than one 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 maintain the initial two items to no more than one ruling each.

- Reason of the study - 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 quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness 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 to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled 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 with every section. If you make the four points listed above, you will need a least of four paragraphs.
Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.

Shape the theory/purpose 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 sound written Procedures segment allows a capable scientist to replacement 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 for the least amount of information that would permit another capable scientist to spare 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 object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text 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:**

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

**Methods:**

- Report the method (not 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 - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

**Approach:**

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in 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 a 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. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently. You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.
Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise 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 in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to 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 part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a 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 implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly 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 with prospect, and let it drop at that.

- Make a decision if each premise is supported, 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 the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One 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 available information
- Submit to work done by specific persons (including you) in past tense.
  - Submit to generally acknowledged facts and main beliefs in present tense.

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- Do not give permission to anyone else to "PROOFREAD" your manuscript.

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**by Global Journals Inc. (US)**

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<tr>
<td>Methods and Procedures</td>
<td>Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads</td>
</tr>
<tr>
<td>Result</td>
<td>Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake</td>
</tr>
<tr>
<td>Discussion</td>
<td>Well organized, Meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited</td>
</tr>
<tr>
<td>References</td>
<td>Complete and correct format, well organized</td>
</tr>
</tbody>
</table>

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### Index

<table>
<thead>
<tr>
<th>Letter</th>
<th>Term</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Acetylcholine</td>
<td>18, 40, 44, 45, 47</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>4, 33, 34</td>
</tr>
<tr>
<td>B</td>
<td>Bilirubin</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>Colorectal</td>
<td>22, 31, 34</td>
</tr>
<tr>
<td>D</td>
<td>Dopaminergic</td>
<td>18, 19, 29, 44</td>
</tr>
<tr>
<td>E</td>
<td>Encephalopathy</td>
<td>1, 5, 6</td>
</tr>
<tr>
<td>F</td>
<td>Flavonoids</td>
<td>12, 13, 14, 16, 17, 21, 22, 23, 25, 26, 27, 28</td>
</tr>
<tr>
<td>G</td>
<td>Ginkgolide</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
<td>1, 3</td>
</tr>
<tr>
<td>H</td>
<td>Hemorrhagic</td>
<td>1, 46</td>
</tr>
<tr>
<td>L</td>
<td>Lavonoids</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Lycopene</td>
<td>30</td>
</tr>
<tr>
<td>M</td>
<td>Macrocephaly</td>
<td>33, 35</td>
</tr>
<tr>
<td></td>
<td>Meningiomas</td>
<td>31, 32, 34, 35</td>
</tr>
<tr>
<td></td>
<td>Myasthenia</td>
<td>44</td>
</tr>
<tr>
<td>N</td>
<td>Necrosis</td>
<td>41</td>
</tr>
<tr>
<td>O</td>
<td>Oedema</td>
<td>1, 3, 4, 9</td>
</tr>
<tr>
<td></td>
<td>Oliguria</td>
<td>1, 2</td>
</tr>
<tr>
<td>P</td>
<td>Pereira</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Polzonetti</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>11, 12, 13, 14, 15, 21</td>
</tr>
<tr>
<td>Q</td>
<td>Quindry</td>
<td>26</td>
</tr>
<tr>
<td>S</td>
<td>Sagrillo</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Scandinavica</td>
<td>36</td>
</tr>
<tr>
<td>V</td>
<td>Vasogenic</td>
<td>1, 3, 4, 8</td>
</tr>
</tbody>
</table>