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Neurology & Nervous System

Reversible Encephalopathy

Assessment on Neuroprotective

Highlights

Presentation of Cowden

The Benefits of Neuroids

Discovering Thoughts, Inventing Future

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

By Abdullah Alasaad, Roaa Amer & Eman Bakhsh
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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

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

Abdullah Alasaad [α], Roaa Amer [σ] & 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 pathognomic 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.

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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), thrombocytopaenia (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/1.73m^2). Serology tests revealed a positive perinuclear antineutrophilic cytoplasmic (p-ANCA), anti-glomerular basement membrane (anti-GBM), and anti-myeloperoxidase 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/1.73m^2 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.

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Appendix

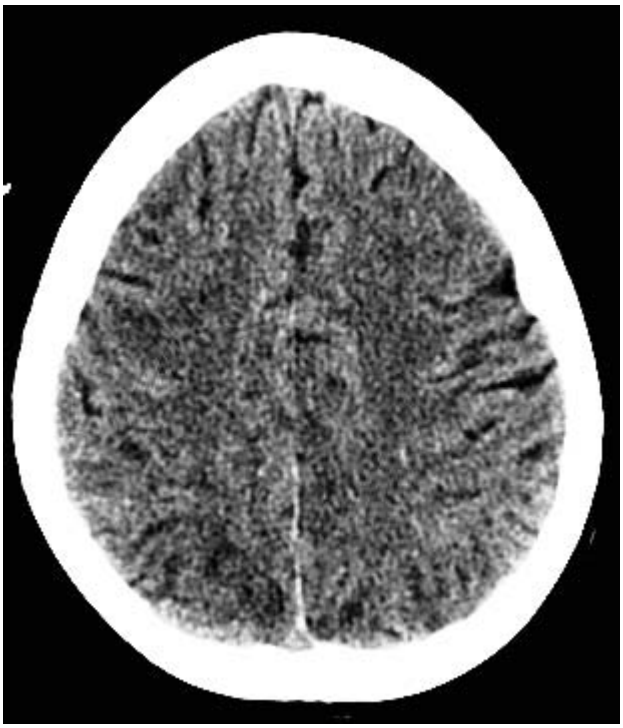

Figure 1A: Axial brain non-enhanced CT image showing multiple right frontal and right parietal subcortical hypodensities

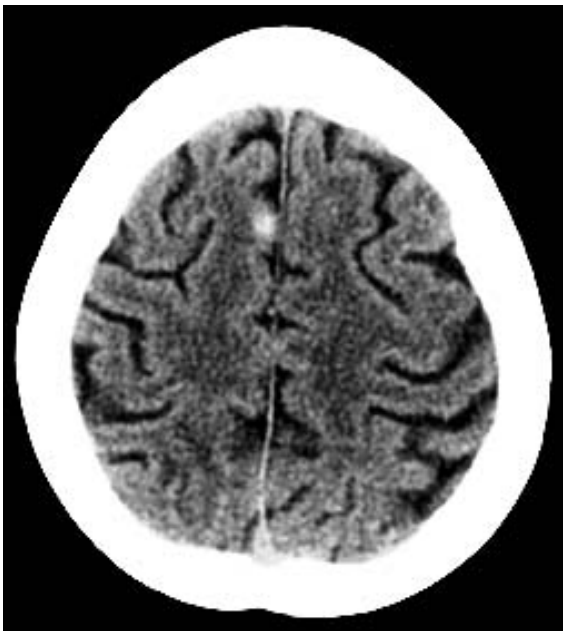

Figure 1B: Axial non-enhanced brain CT image showing focal rounded hyperdensities in the medial aspect of the right frontal cortex consistent with cortical bleeding

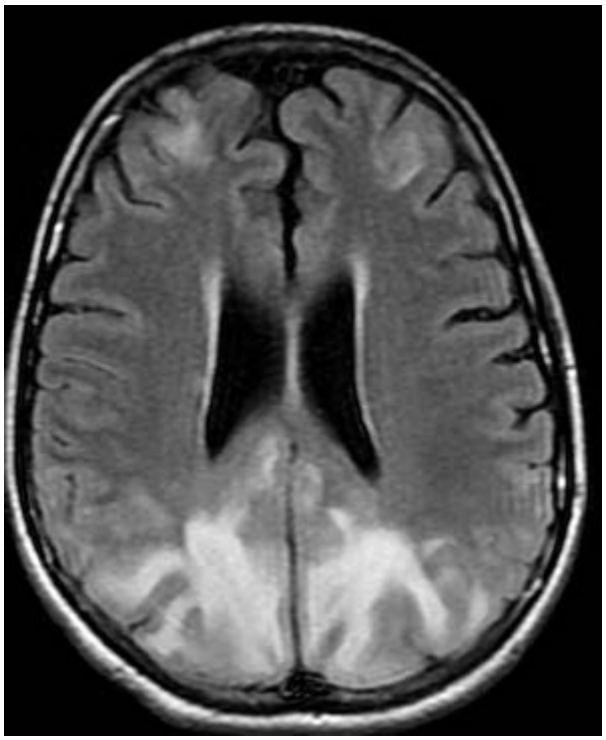

Figure 2A: Brain MRI axial FLAIR sequence demonstrating bilateral symmetrical cortical and subcortical high T2 signal in the frontal and parietal lobes

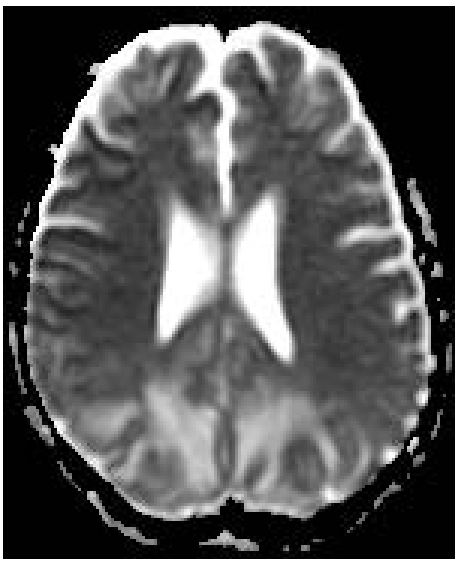

Figure 2B: Axial ADC map showing high ADC signal in the parietal lobes indicating vasogenic oedema

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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

Sao Francisco University

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

Strictly as per the compliance and regulations of:

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

Ana Carolina Bombardi Duarte [α], Maycon Giovani Santanai [σ], Gulhermedi Camilo Orfalii [ρ], Carlos Tadeu Parisi de Oliveira [ω] & Denise Gonçalves Priolli [¥]

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I. 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 diet[1]. These compounds have shown low toxicity as well as a variety of physiological effects[1]. 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 effects[2], as well as presenting low toxicity to human organism[1,3]. 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 pathways[1]. Structurally, flavonoids are composed of a basic flavylium cation, with three phenolic rings[4]. 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 [1,5]. 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 [1,4,6–8].

Flavonoids neuroprotective effects are mostly bound to its related antioxidant, anti-proliferative and anti-inflammatory properties[9,10]. 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 metals[1]. In addition, because of inefficient antioxidant defense mechanisms, alterations of neuronal organic homeostasis can cause grave repercussions[1,9]. 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 [2,11,12]. 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, Parkinson's and Huntington's disease cause a progressive functional alteration of neuronal systems[13]. Worldwide, they present variable incidence and constantly relate to high morbidity rates, higher cost in health care and social impairment[13–15]. 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[9,13,16–22]. 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[23]. 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) *Litterature Review*

This paper was based on a literature search of PubMed and Scielo databases using keyword combinations "Flavonoids+Neuroprotecition"; "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[25]. Recommendation levels are the results of extensive research analysis and an important guide to practitioner's clinical decisions[26]. 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.

Table 1: Evidence Level adapted from Oxford CEBM to evaluate therapeutic value of scientific studies.

LEVEL	THERAPY
1A	Systematic Reviews of Randomized Controlled Trials (RCT)
1B	Individual RCT with narrow Confidence Interval
1C	All or None Studies
1D*	*In Vivo* Animal Trials
2A	Systematic Reviews of Cohort Studies
2B*	I. Cohort Studies (*In Human*)
	II. *Ex Vivo* Studies
2C*	Outcome Research or Ecological Studies or *In Vitro* Studies
3A	Systematic Review of Case-Control Studies
3B*	Case-Control Studies or Drug Biological Characteristics Assessment Studies
4*	Case-series and poor quality cohort and case-control studies or Literature Review
5	Expert opinion without explicit critical appraisal
*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[1]. Amongst flavonols 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 quercetin-3-monoglucoside[1,31].

Flavonoids absorption occur predominantly in the small intestine, however it is limited by molecular weight and hydrophilicity[1,31]. Few studies have been conducted as to elucidate bioavailability and absorption across the blood-brain barrierin human models[32,33] **(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[34].

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[1,34]. Onions, kale, broccoli and apples are important sources of glucoside molecules, such as Rutin[35]. IQ is a common naturally occurring glycoside also obtained by enzymatic hydrolysis of rutin with hesperedinase, an enzyme produced by specific types of fungisuch as *Penicillium sp.*

Heperedinase has a α-l-ramnosidase 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[36]. 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[36]. Studies have shown the superiority of anti-oxidant and anti-proliferative properties of HR when compared solely to quercetin and rutin **(Evidence Level 2C)**[36,37].

III. Neurodegenerative Diseases

Neurodegenerative diseases are a consequence of genetic and environmental factors that are strongly associated with age[38]. These disorders arise from multifactorial conditions that interfere directly with cellular oxidative homeostasis and function[38]. 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)[38]. Also appearing to command numerous neuronal pathways, leading to alterations in neurotransmission and ionic channels, protein aggregation, impaired bioenergetics and even cellular death[38].

Free radicals are indispensable molecules to cellular function by involvement in many biochemical activities[39]. However, oxidative stress arise from disturbances between pro-oxidant/antioxidant equilibrium[39]. Overproduction of free radicals produce cytotoxicity and genotoxicity by damaging biomolecules, such as proteins, lipids and DNA[39] and leading to arise of various chronic diseases, including in the CNS[39]. In the brain glial and neuronal cells are particularly sensitive to free radicals and actively targeted by ROS[39]. 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)**[2,9,40–43]. Also exhibiting activation of anti-oxidant enzymes (**Evidence Level 1B)**[44] **(Evidence Level 2C)**[45,46], protein disaggregation and diminished production **(Evidence Level 2C)**[47], decrease of lipid peroxidation **(Evidence Level 1B)**[48] **(Evidence Level 2C)**[42], transitional metal chelation **(Evidence Level 2C e 4)**[2,49–51] and anti-inflammation effects **(Evidence Level 1B)**[52]. 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 β-amyloid plaques (major constituent of senile plaques), intracellular neurofibrillary tangles, tau protein phosphorylation and neurodegeneration of synaptic neurons, especially in the hippocampus[13,53].Oxidative stress and neuro-inflammation are also considered hallmarks of AD, mainly responsible for increasedneurotoxicity[54] of cognitive-modulating areas [55]. In addition, the decrease in cholinergic neurotransmission has also been implicated in cognitive decline and behavioral changes of AD[56].

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 kaempferol[57]. 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)**[58].

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 hippocampus[47], 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)**[59]**.** 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 Level2C)**[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 Level2C)**[47]. In addition, **Choi et al. (2014)** studied the*in vitro* activity of a flavonoid panel, including quercetin and rutin, against Abeta-induced toxicity. Results corroborated previous studies showing that flavonoids significantly block Aβ-induced neuronal toxicity**(Evidence Level 2C)**[61].

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)**[63,64], and the production of ROS and LDH were decreased, as an increase on superoxide dismutase occurred **(Evidence Level2C)**[63]. **Mohebali et al., 2016** demonstrated both Rutin's and Quercetin's potential to down regulate inflammation-involved genes in AD**(Evidence Level 1D.I)**[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, astrogliosis 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[56]. The increase on cholinergic neurotransmission is an important focus of recent drug therapy and comprises the inhibition of acetylcholinesterase (AchE), acetylcholine's degrading enzyme [71]. 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 then some of the drugs in the market, like Donezepil[74]; also acting in a dose-dependent manner**(Evidence Level 3B)**[42]. Rutin also seems to show AchE inhibition properties**(Evidence Level 3B)**[75],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 activity[76] and has been implied as a promising molecule for the treatment of several pathologies, especially cancer[77]**.**

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-inflammation[22]. Pathogenic aspects of PD involve mitochondrial dysfunction, changes in micro-RNA and α-synuclein levels[13], a major constituent of Lewy bodies and a hallmark of PD[78]. Oxidative stress has been

associated as a risk factor for dopamine cellular degeneration of PD[79], and mitochondrial dysfunction plays an important role on energetic balance as well as regulating oxidative and apoptotic pathways[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)**[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)**[81].

Other studies using methyl-4-phenylpyridinium ion (MPP(+)), a parkinsonian toxin that provokes degeneration of dopaminergic neurons[82], and 6-hydroxydopamine (6-OHDA), a selective dopaminergic neurotoxin[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-α and COX-2) on microglial cells **(Evidence Levels 2C, 2C, 1D, 1D)**[82–85]. 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)**[60].

In addition, in 2015, Ahn et al. investigated quercetin's specific effect on α-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 α-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)**[78].

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)**[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)**[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[89]. Incidence is higher at European countries and mean age of symptoms onset occurs around 40 years old [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[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)**[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 throughlessening 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)**[93,94].

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

	Study	*Year*	*Flavonoid Tested*	*ARRIVE Checklist Items Met*	*ARRIVE Checklist Items Not-Met*
Alzheimer's Disease	Liu et al.[62]	2013	Quercetin	1-9, 10a, 11b, 12-20	10b, 11a
	Hayakawa et al.[64]	2015	Quercetin	1,2,3a, 4-9, 11-13, 15-20	3b, 10, 14
	Sabogal-Guaqueta et al.[66]	2015	Quercetin	1,2,3a, 4-8,11b, 12,13, 16-20	3b, 8a, 10, 11a, 14,15
	Javed et al.[67]	2012	Rutin	1, 2, 3a, 4-9, 10a, 12, 13, 15-20	3b, 10b, 10c, 11, 14
	Choi et al.[68]	2015	Rutin	1-9, 10a, 11-20	10b, 10c
	Xu et al.[69]	2014	Rutin	1, 2, 3a, 4-9, 10a, 11-13, 15-20	3b, 10b, 10c, 14
	Moghbelinejad et al.[70]	2014	Rutin	1,2,3a, 4, 5, 6a, 6c, 7, 8b, 9, 12, 13, 15-20	3b, 6b, 8a, 10, 11, 14
	Abdalla et al[72]	2014	Quercetin	1-9, 10a, 11-19	10b, 10c, 20
Parkinson's Disease	Karuppagounder et al.[80]	2013	Quercetin	1-9, 12-14, 16, 17-20	10, 11, 15
	Zhang et al.[83]	2011	Quercetin	1-5, 8, 10, 12-14, 16-20	6, 7, 9, 11, 15
	Haleagrahara et al.[85]	2013	Quercetin	1-20	-
Huntington's Disease	Jain et al.[93]	2014	Quercetin	1, 2, 3a, 4-20	3b
	Chakraborty et al.[94]	2014	Quercetin	1-5, 6a, 6b, 7-10, 12-14, 16-20	6c, 11, 15

IV. Conclusion

Flavonoids have been widely investigated in the past decades and have shown a wide variety of physiological effects, determining a therapeutic potential on innumerous diseases, including neurological pathologies. Their neuroprotective effects are mostly related to anti-oxidant and anti-inflammatory properties; however, specific mechanisms have been reached on both *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 which the goal is 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 seems 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.

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Cerebellar Dysplastic Gangliocytoma as the First Presentation of Cowden Syndrome

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Abdulrhman Alnasser [α], Roaa Amer [σ] & Eman Bakhsh [ρ]

Abstract- Cowden syndrome is a rare autosomal-dominant disease characterized by multisystem hamartomas usually affecting the skin, thyroid gland, breast, and gastrointestinal tract; these hamartomastend 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 previous2 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 preventedor 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.

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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 brainrevealed 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 (Figure2). 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 polypectomy 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 $\leq$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.

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Figures

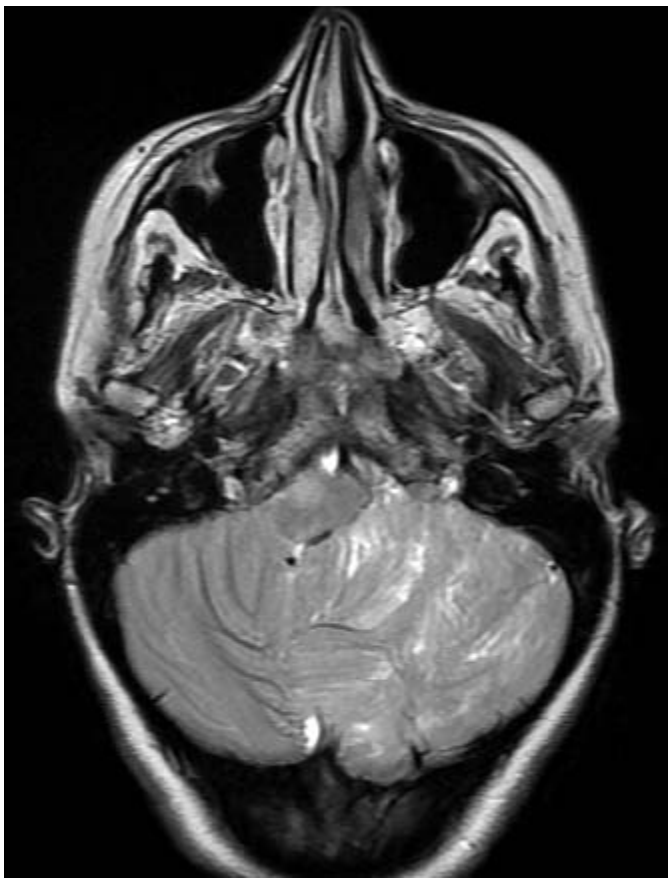

Figure 1A: Axial T2-weighted magnetic resonance imaging of the brain showing the left cerebellar mass with widened cerebellar folia, a striated pattern, and preserved cortex. Note the retroclivaldural-based isointense mass on the right side representing retroclival meningioma.

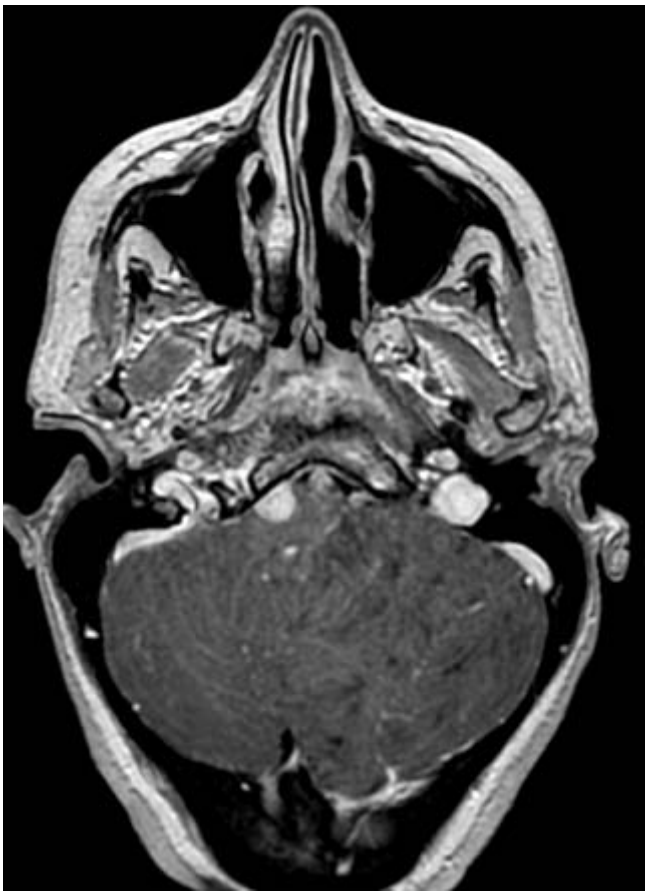

Figure 1B: Post-contrast axial spoiled gradient echo images of the brain showing no enhancement in the left cerebellar mass. Note the intensely enhancing retroclival lesions representing meningioma.

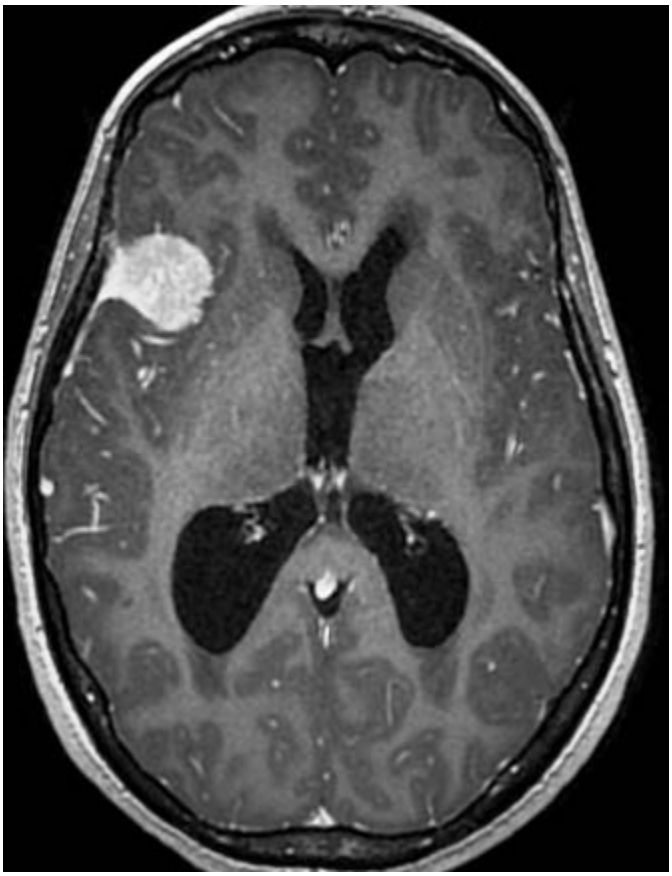

Figure 1: Post-contrast axial spoiled gradient echo images of the brain showing adural-based, intensely enhancing extra-axial mass in the right temporal region representing meningioma. Note the dilated lateral ventricles representing hydrocephalus caused by the previously described left cerebellar mass.

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The Benefits of Neuroids/Neuropeptides in Combating Cerebrovascular, Neurological and Ocular Diseases

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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., phosphatidylcho-line, 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 OS2 (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.

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Diagnosis can begin with aauscultation 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].

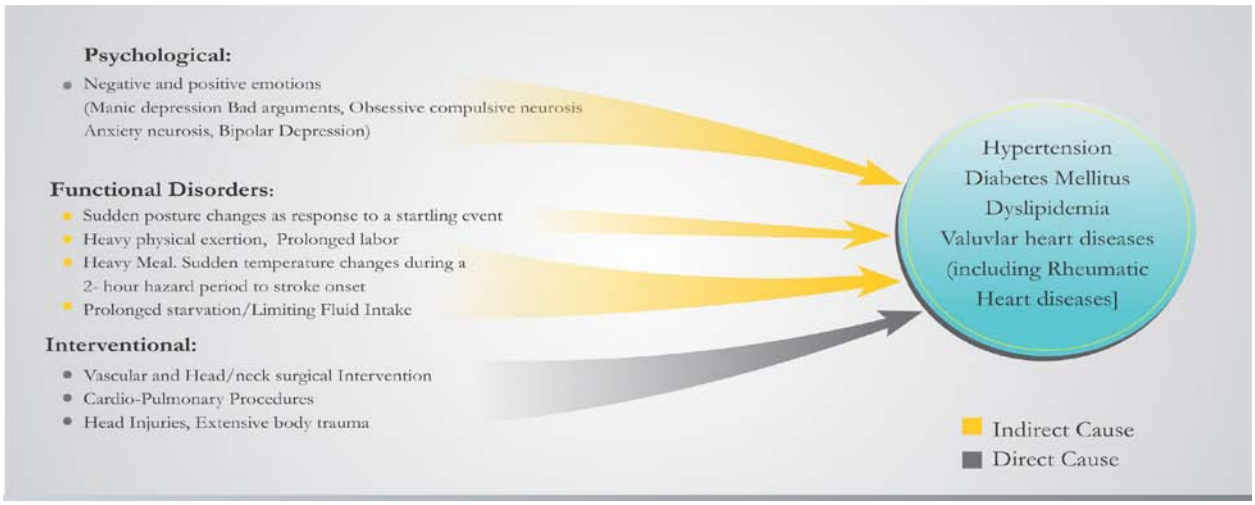

Figure 1: Direct and Indirect triggering factors

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 (Phospitadylcholines), 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).

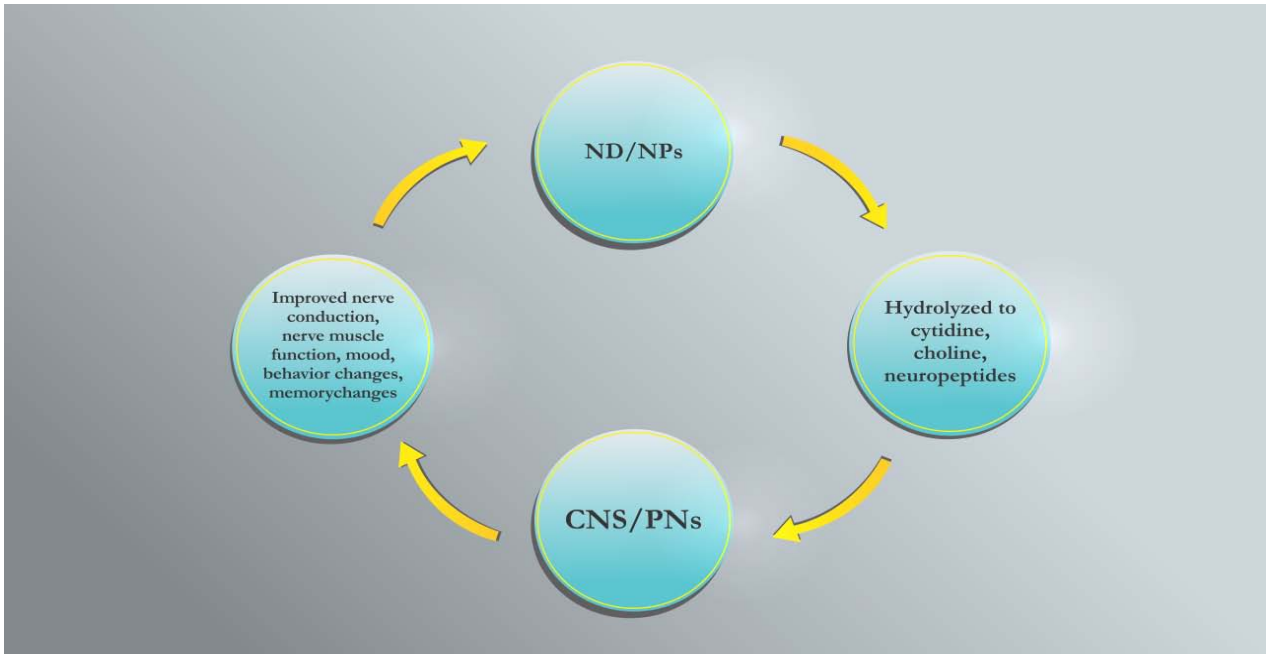

Figure 2: Life Cycle of Neuroids and Neuropeptides (ND/NPs)

*CNS=central nervous system (including brain)
*PNs=Peripheral nerves

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 developenent 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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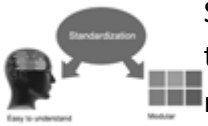

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4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

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Original research paper: Such papers are reports of high-level significant original research work.

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The recommended size of original research paper is less than seven thousand words, review papers fewer than seven thousands words also.Preparation of research paper or how to write research paper, are major hurdle, while writing manuscript. The research articles and research letters should be fewer than three thousand words, the structure original research paper; sometime review paper should be as follows:

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(c) Up to ten keywords, that precisely identifies the paper's subject, purpose, and focus.

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(e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition; sources of information must be given and numerical methods must be specified by reference, unless non-standard.

(f) Results should be presented concisely, by well-designed tables and/or figures; the same data may not be used in both; suitable statistical data should be given. All data must be obtained with attention to numerical detail in the planning stage. As reproduced design has been recognized to be important to experiments for a considerable time, the Editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un-refereed;

(g) Discussion should cover the implications and consequences, not just recapitulating the results; conclusions should be summarizing.

(h) Brief Acknowledgements.

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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.

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- One should avoid outdated words.

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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.

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TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

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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 straight forward. 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.

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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.

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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.

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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.

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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.

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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.

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To make a paper clear

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· 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

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· Shun use of extra pictures - include only those figures essential to presenting results

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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.

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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.

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- 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
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- Center on shortening results - bound background information to a verdict or two, if completely necessary
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- 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

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- 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:

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- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

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Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
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- 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.

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- 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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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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