Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: A

Neurology & Nervous System

Strokes in Black Africa

Pilot Study Revealed Association

Highlights

Impact of Gender on Dementia

Healing of Neurological Disorders

Discovering Thoughts, Inventing Future

VOLUME 16 ISSUE 2 VERSION 1.0

Global Journal of Medical Research: A
Neurology and Nervous System

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Volume 16 Issue 2 (Ver. 1.0)

Open Association of Research Society

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

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Sponsors: Open Association of Research Society
Open Scientific Standards

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Framingham Massachusetts Pin: 01701,
United States of America
USA Toll Free: +001-888-839-7392
USA Toll Free Fax: +001-888-839-7392

Offset Typesetting

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Packaging & Continental Dispatching

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Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Healing of Neurological Disorders with Bio Electron's Photons

By Nick Kostovic

Kostovic Acupuncture by Bio Electrons Laser, United States

Introduction- Before I begin the cases below, let me explain what and how this Kostovic Biotechnological Energetic Medical Laser Device, K-BTE works. The K-BTE Device is created in a proprietary method, we've assembled in a special circuitry 120volts of Dc/Ac/ Reverse(canceling the magnetic from the electric) which then is transferred through water. After deleting the magnetic aspect we extract the bio electrons from this water (electric fluid), controlling their direction and strength(micro and nano amperes frequency). Lastly we add in extracted electrons enriched with a number of natural acids. We incorporate these natural acids into our Biological Agents Device.

Knowing the human body's resistance to the ground is 1,000 Ohms (dry) yet using 120 voltages of AC we very safely produce the gentle effect of 12-15 Micro Amperes (DC). By utilizing this newly discovered Reverse Current and separating electro from magnetic we easily prevent electromagnetic shock. Our K-BTE device utilizing these gentle Micro Amperes frequencies can effectively burn and disperse oxidized proteins from the body. This frequency is 10,000 times less in strength than today's developed laser technology. These energetic acupuncture type penetrations on the surface of the skin are soft, not at all an electric shock.

GJMR- A Classification: NLMC Code: WM 475

HEALINGOFNEUROLOGICALDISORDERSWITHBIOELECTRONSPHOTONS

Strictly as per the compliance and regulations of:

Healing of Neurological Disorders with Bio Electron's Photons

Nick Kostovic

I. Introduction

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The new invented laser medical device Kostovic Biotechnological Energizer, called K-BTE correlates to the energetic fields that already exist in nature, but in more effective form. The mineral granite fields surrounded by ice, caused by low temperature in nature, radiate strong elementary energy. The irradiated elementary energy from mineral fields interacts with complex elementary biochemical energy charges from the sun's rays. It is well known that these fields exist in the far regions of Earth.

Author: *Kostovic Acupuncture by Bio Electrons Laser, Corp.*
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For example, some of these extraordinary energy fields are found on the slopes of Himalayas. These areas attract extremely powerful, complex and rich sun's ray elementary biochemical energy charges from nature and can contribute to a longer lasting and healthier life. For this reason, some people in these areas live extended lives, up to one hundred years or more and are not prone to most degenerative diseases.

Kostovic -Biotechnological Energizer, K-BTE medical laser device creates a powerful energetic vibration through its field that is capable to attract these elementary biochemical charges and the electron neutrinos, which are more effective, form than extraordinary fields on the Earth, as the slopes of Himalayas.

The durability of rudiment of cellular components is directly dependent on the attracted new elementary biochemical charges and electron neutrinos. Released elementary biochemical charges and electron neutrinos are the only ones in the form of the elemental energetic values. These are capable of nourishing and rebuilding the cellular components into central nervous system. Enzyme proteins are enriched, and the oxidized proteins are unmistakably "burned off". The rudiment of cellular components is consist of DNA, proteins and lipids as chemical element. Its recovery depends exclusively on attracted elemental biochemical energetic values.

The Center has further continued research and development of the transfer of the different elementary energy values from nature through hairs and skin (hairs are the offshoot of central nervous system), directly into the cellular components of the brain. Due to the stimulation of the pineal gland in the brain, this process is visible with the closed eyes.

On a daily basis our cells are always being born and dying. When we are young our bodies can disperse and get rid of all the dead cells. We have cells that eat these dead oxidized proteins. But with aging the dead cells are produced faster than the aging body can get rid of. When the oxygen and protein rich blood supply is prevented from reaching and feeding the muscle fibers due to this build up of dead cells, then the nourishing proteins become oxidized proteins.

These oxidized proteins become our number 1 enemy, as they attract parasites, microbes and bacterias etc. So now the human body not only has dying fiber tissue, the building blocks of muscle tissue

but we also have diseases developing. If we are not able to clean this declining fiber tissue from the dead cells and oxidized proteins, then the tissue will die, creating a domino like effect killing more and more fiber tissues, the building blocks of the organs.

For the first time in history our discovery enables us to maintain the physical organs. We do this by first cleansing the fiber tissues, burning away the dead cells and oxidized proteins with our wireless acupuncture therapy. After we have burned away the dead cells and oxidized proteins making space for the healthy blood supply to finally reach the fiber tissues, then body can rebuild healthy fiber tissue.

The K-BTE Medical Laser Device is always preformed in three phases which is why it is so highly efficient in improving and healing the different types of neurological and physical disorders. As I have stated first we wirelessly send biochemical electrical impulses into the diseased fiber tissue of injured areas to "burn off" the oxidized proteins, unhealthy and malignant cells from the healthy cells, enabling the body to easily excrete them.

While wirelessly sending these photons of bio electrons through the patient's skin to burn away the diseased areas, we are also burning away any plaque within the vascular system that is supplying this area. Thereby eliminating clots in vascular system, enabling the injured and healthy cells to fully receive the healthy blood supply of oxygen and proteins.

After we have cleansed the area with the bio electrical electricity, the second process is using the Biological Agent Device. This Biological Agent Device releases sheaves of elementary laser beams of biological electricity with enriched electrons. We enrich the electrons with biological and mineral agents such as gold, silver and pyrite-Fe2 and converted amino acids. We use various natural acid liquids such as virgin olive oil, fig acid, and lemon, etc., ("values of different energetic conductors") into an energetic form of enriched electrons. The virgin olive oil contains natural acids, Oleic and Linoleic which are considered antioxidants, not saturated fats, like polyphenol.

These ingredients are very important in the *protection of healthy cells from destructible free radicals.* We biochemically charge these natural acids converting them into a *light* wrapping which surrounds the electrons. Extracted from the H20 electric fluid and coated with the converted natural acids (light charged), these electrons become bio electron photons which we are capable to absolutely control and direct into the patient's tissue, nourishing and invigorating the healthy cells.

The final segment of this therapy, is very intricate. I have many documents on my website that delve into greater detail. This Center has continued in-depth research and development of the laser's transfer of the different elementary energy values from nature through the hair and skin pores (hairs are the offshoots of the central nervous system), directly into the cellular components of the brain. In this final segment the therapist touches the client's forehead with his/her index fingers which stimulates the pineal gland in the brain, this laser process is easily visible with the patients closed eyes.

The therapist transfers the biological electricity in the form of different energetic vibrations by pressing his/her fingers on the patient's forehead, scalp and skin releasing this bio electric vibration which supplies throughout the recently cleansed brain with more of the finest/slightest bio photon elemental energy.

This finest bio photon elemental energy interacts with the brain enabling/reflecting surplus weaker elemental energy to irradiate out from the brain creating an aura of elemental energy. This aura around the outside of the calvarium/skull becomes the catalyst for attracting more elemental biophoton particles of sunlight directly into the brain. These elemental bio photon sunlight particles (which can't be seen with the naked eye) surrounds us in nature and now for the first time in history we can attract and direct them. This surplus of weaker elemental brain irradiation now circulating in an aura outside of the skull appears to the patient's open eyes as a wavy blurry view. Our ability to attract these bio photon sunlight particles directly into the brain provokes/awakens passive, dormant, hibernating brain nerve cells. As we awaken the passive/hibernating brain nerve cells we are simultaneously nourishing and feeding any damaged and weaken areas thereby regenerating these harmed and injured areas in the brain.

The healing process to the brain's nerve cells gradually become visible to the patient by this special way of attracting elementary biochemical bio photon charges. With closed eyes the patient sees circles of many colors including white, black, blue, green, red, rose, yellow, turquoise, purple, orange and gold as the body absorbs the elementary biochemical bio photon charges awakening billions of hibernating passive brain nerve cells converting them into newly activated brain nerve cells.

When dormant, passive brain nerve cells now become newly activated brain nerve cells, the brain can then successfully combat the causes of most neurological disorders and traumatic brain injuries. Simultaneously, while the newly activated brain nerve cells (the former passive, dormant brain nerve cells) are being strengthened and invigorated they are now creating improvement in the neuronal functioning plus increasing neuronal production and improving the various nerve impulses throughout the body.

The mobility and movements of the arms, legs, spine etc, reacquire their normal function, since the neuronal activity has been repaired, the body is restored. The results are notable, the mitigation of

immobility displays the improvement for the patients suffering from this horrible disease. In their dormant form these passive brain nerve cells are resistant and indestructible to all neurological illnesses. The passive brain nerve cells are slight and very sensitive and contain faint energy charges which can only be stimulated/awakened by attracting to them the finest elementary biochemical energy charges through this very slight form of energetic vibrations.

II. ALS Treatment

ALS (Aumyotropic Lateral Sclerosis) is a disorder of the motor neurons which are responsible for contracting skeletal muscles. The body's organ muscles start to atrophy, loosing functionality and with some paralysis begins. The varying degrees of this illness affect gradually two groups of motor neurons. One group of motor neurons results in the immobility of the extremities and other in the form of paralysis in some organs. The characteristic symptoms of ALS eventually appear as a weakened neuronal structure. ALS is most likely well established by the time the patient first notices muscles weakness, shortness of breath, reduced ability to swallow, decreased mobility etc. As we perform our Bio-electric surgery and therapy on ALS sufferers, releasing bio electron's photons enriched with natural acids into the brain,. The damaged areas are easily revealed due to the fact that the infected areas in the brain are quite painful when touched with our bio energetic acupuncture technique. Using two agents, one from minerals such as gold, silver, or pyrite and the other from biological agents such as lemons, fig acids and fish bones we simultaneously send the bio electron's photons enriched with these natural acids into the brain. As they penetrate throughout the brain the unhealthy cells from the damaged areas begin a "burning off" process enabling them now to be easily excreted from the body. The ALS damaged areas in the brain are a source of aggressive "dying off" of active brain nerve cells. We are able to prevent this condition from further neuronal deterioration and non functioning of motor impulses. Our results are a notable process due to the mitigation of further immobility as well as paralysis. For some clients we can completely bring back the body's normal functioning again.

Treatment plans for ALS patients are a minimum of one year with daily sessions of 50 minutes at least 6 days a week. Daily sessions could consist of more than one 50 minute treatment per day. Treatment plans are determined by the severity of their condition. After the treatment plan has been completed it is necessary to have a yearly follow up of at least one month. It is strongly recommended to have this yearly clean-up to refresh those formerly affected weakened areas of the ALS. These patients who have had the bio-electric therapy benefit greatly especially since it is also preventive to paralysis. The duration of recovery and improvement is long lasting but follow-ups are imperative to keep those dead cells from piling up again. Though the enriched bio electron's photons released has the capability of regaining neuronal motor impulses many wheelchair bound patients still need to get physical therapy to rebuild those atrophied muscles so they can finally get out of the wheelchair.

III. ALS Berbery Type Case

The patient A. was diagnosed with ALS Berbery type in June 2001. He was seen by the top ALS expert at UCLA in August 2001. The doctors informed the patient that his CO2 would measure 45 points within 6 months which would cause suffocation. The doctor's predicted this progressive disease would end his life by January 2002. The UCLA doctors informed him that any technology for preventing the growth of the CO2 had not been developed yet. Fortunately patient A. found our center. We stand alone in our technology since we are able to clean his physical organs from CO2, nerve's biochemical toxic gases, radioactive radiations, etc. Medical doctors have yet to match our technology. Which is why the FDA has approved our laser medical device and given it a classification of it's own.

UCLA offered the patient an experimental drug called Rilutek. The prescribed drug would somehow subside suffocation, but the side effects would compromise his liver and kidney functions. The drug, with these side effects, could not extend the patients life beyond 6 months which matched his CO2 prognosis. Fortunately the patient A declined the medication.

Patient A. suffered from ALS-Berbery type, beside the difficulty breathing and swallowing his symptoms included falling down. Patient A. came to the Biotechnological Health Center January 13, 2002. Hopeless and near death he was desperately looking for help. He had heard that I helped a patient suffering from ALS who's mobility was restored after the K-BTE treatments. With this type of ALS- Berbery - CO2 levels were at 43 points which is extremely high for the lungs. As noted, this level of CO2 would naturally increase and eventually cause suffocation. Within 10 days of treatments his CO2 was decreased by one point bringing it to 42. The treatments were performed directly into the chest area simultaneously from front and the back. The patient released by coughing up colorless, sticky layers of compressed mucous. By releasing these elementary laser's beams of enriched bio electron's photons of the biological electricity into the skin and then into the blood vessels in the lungs we started the process of cleaning. After 1 month of sessions his CO2 decreased and his muscle structure was strengthened. After 180 treatments the CO2 was lowered to 28 which is normal, and it never increased again. We also treated the throat area, strengthening the nodules on the vocal

cords thus recovering speech, rejuvenating the esophagus tissues and restoring the ability to swallow. By treating the neck area his head was able to become straightened to its normal vertical position within one month. Arms and legs were restored from atrophy and restored the existing areas from paralysis. After 18 months the patient's results were notable, walking, laughing, speaking, swallowing, his entire metabolic condition improved. His life was extended 8 years. But unfortunately, Patient A did not commit to the recommended follow-ups.

IV. Parkinson's Disease Case

Parkinson's disease affects the neurons that control the complex performance of body movements. Their decline causes weakness and the patient experiences tremors in the arms and legs gradually becoming paralyzed.

Patient B. is a 80 year old man with Parkinson's Disease: The patient had tremors in both arms and his right leg causing aggravated mobility. UCLA medical doctors prescribed a combination of levodopa and carbidopa which is used to treat the symptoms of Parkinson's Disease. The drugs didn't help, and the UCLA doctors didn't have any other technological healing options. The patient was not satisfied with the traditional treatment plan so he sought treatment at The Biotechnological Health Center, Inc. His active brain nerve cells were strengthened by the penetrating enriched bio electron's photons in the form of elementary needles of energetic acupuncture. The passive brain nerve cells were awakened by the elemental biochemical charges of different energetic vibrations. We successfully reversed his nerve damage and reversed the muscle damage. Patient B's arms and legs were restored from tremors thus returning to his normal mobile function. His symptoms were completely eliminated confirming our results as notable and worthy of attention from the medical community. The enriched bio electron's photons of bio-electricity also renewed Patient B's weakened and sore knee tissues, bone and soft cartilage.

Patient B's testimony which was written after his recovery can be found on my website. In addition, his testimony was filmed by Croatian National Television. Patient B. is first case in the world cured from Parkinson's diseases.

V. Treatment for Alzheimer's

Alzheimer's disease affects the memory and intelligence. Patients become unable to recognize the closest of family members and their environment. Treatments plan is a minimum of 1 year, 6 days per week with 50 minute sessions, we think double sessions each day can speed up the recovery time.

The damaged areas of the brain caused by Alzheimer's disease are treated as I explained earlier with striking the skull with enriched bio electron's photons in the form of elementary needles of energetic acupuncture through biological agents.

As noted, the bio photon energy wirelessly penetrates through the skin directly into the sickened areas deep into the brain, targeting the sources of the illness. The biological electricity is enriched with amino acids of Virgin olive oil etc which is converted into an energetic form of enriched bio electron's photons. These enriched amino acids in the biological agents penetrate into the brain revealing the damaged brain areas, the sources of the disease which we gently yet powerfully destroy. Modern science hasn't yet discovered the causes of Alzheimer's disease as well as most neurological disorders, yet we can easily can find the exact damaged areas deep into the brain, because they are painful. Directing these sheaves of enriched electrons into these painful areas we destroy and excrete these unhealthy cells from the brain. We know improvements are made when the pain level had decreased, neuronal functioning is restored and the patient reports that memory and intelligence has definitely improved.

VI. MS Disease Case

Patient C. is a 33 years old female patient from Zagreb, Croatia. She suffered from an extremely progressive type of multiple sclerosis. Her symptoms included lose of balance and falling down. After nineteen weeks of treatments the patient was recovered to normal balance.

MS disorder is caused by inflammation of the myelin sheath which causes impairment and a decline of motor neuron functioning. Gradually the muscular system becomes paralyzed, diminishing the patient's mobility. Using the same technique of intensive therapy by the K-TBE laser medical device, releasing enriched bio electron's photons into the body, the patient's legs and arms muscle impairment was reversed and mobility was restored. In addition, the blood circulation returned to these areas and reflexes were restored and active. These improvements were accomplished by regenerating active and awakening passive/hibernating brain nerve cells with the elemental biochemical values. The damaged areas of the brain and spinal cord were struck with enriched bio electron's photons of biological electricity. The sources of the MS disease were destroyed and dispersed without any negative side effects. It is important to point out that in this case the painful spots were detected deep in the brain confirming inflammation of the myelin sheath which caused the impairment of the spinal cord fluid from reaching the brain. We completely reversed the nerve damage as well as we reversed the muscle weakness and patient C. is

now free of the disease. Testimonials from Zagreb, Croatia is written by Prof. Dr. Zlatko Drvar and can be found in preface of my book "Universe God's Jewel".

a) *The Patient C. is first case in the world cured from MS*

MS, Neuropathy and Dementia treatments take approximately 6 months with 50 minutes sessions, 5 days a week. Intervals between device use is not necessary or recommended. Regaining mobility with significant degrees of improvement and reversing muscle weakness is unheard of. After our treatments are completed if a patient has been in a wheelchair for a while then physical therapy is imperative to regain muscle strength in the atrophied muscles in order to walk without the wheelchair or a cane. Duration of the restored health condition is long lasting with advised once a year follow up treatments.

On our website we have testimonials and medical records which will validate the results with substantial scientific evidence. The K-BTE Medical Laser Device performs this bio-electric surgery and therapy providing clinically significant improvement in patients illnesses based on significant and valid scientific evidence. While at the same time, this device poses no risk of illness or injury to any healthy cells. This therapy is highly successful in the recuperation from these diseases and offers significant mitigation of symptoms. Additionally, this advanced technological discovery is an adjunct to early diagnosis of various illnesses. It is capable of detecting and revealing painful areas in the brain or any other physical organ before they even show up on MRI's or CAT SCANS. The K-BTE device keenly reveals the damaged areas affected with unhealthy cells. MRI's and other diagnostic equipment are not always able to detect the early origin of many diseases, but we are able to penetrate and with precision to locate the damaged unhealthy areas. After each treatment the pain immediately subsides. Once the cleaning process is completed, the once affected areas with unhealthy cells is no longer painful and treatments now start to feel comfortable. The duration of treatments for eliminating tumors and malignant cancers could be from 2 to 6 months, we consider this as short term use. Neurological Disorders including some of the most difficult cases are a minimum of 6 months to one year or more, we consider this long term use.

For patients with any recent surgical procedures we do not recommend having the K-BTE treatment. Although the K-BTE device is capable of performing on open wounds and does help in speeding up the recovery time, we restrict our treatment until the patient has recovered from their previous surgery.

According to official statistics, 60 million US citizens are suffering from 600 hundred different types of neurological disorders. Utilizing the K-BTE device's bio-electric surgery and therapy we are capable of significantly improving the cognitive functioning, memory and mobility of many of these neurological disorders.

The K-BTE medical laser device is extremely capable to mitigate many symptoms associated with these 600 different neurological diseases as well as eliminating a number of these disorders.

This KBTE Device can prevent diseases from developing, including neurological diseases, cancer, stroke and heart disease as well as restore those afflicted with these diseases making their lives healthy, vital and longer lasting.

The Kostovic Health Center has 17 years of research and studies of helping incapacitated ALS, Alzheimers and MS patients regain the use of their limbs and no longer needing wheelchairs after only months of this unique therapy. Some we completely healed but most of them we absolutely improved their health, which modern science today is unable to do. Modern science attests to the fact that they might be able to slow down the progression but have never improved their symptoms nor stopped the deterioration of motor skills and declining brain functioning.

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Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Strokes in Black Africa

By Kokou Mensah Guinhouya, Nyinevi Anayo, Léhleng Agba, Mofou Belo & A. A. Koffi Balogou

Universite de Lome

Abstract- The study of strokes in Africa bears at the same time an epidemiological, etiological, semiological and therapeutical interest. The studies made on the black continent [11] these early thirty years show the necessity in this sector which remains unexplored, to evaluate the incidence and the prevalence of stroke in order to elaborate programmes and research protocols adapted to our realities. However, it is difficult to have a coherent interpretation of the results of these studies because of the high variability of epidemiological clues.

In black Aflica, in Nigeria [1], the prevalence of strokes was 60,67/100.000 persons. These rates of prevalence observed in Africa go against the rate reported in industrialised countries 145/100.000 persons [2] and could suggest the existence of some particularities that are special to Africa continent.

GJMR- A Classification: *NLMC Code: WL 356*

STROKESINBLACKAFRICA

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Strokes in Black Africa

Kokou Mensah Guinhouya [α], Nyinevi Anayo [σ], Léhleng Agba [ρ], Mofou Belo [ω] & A. A. Koffi Balogou [¥]

I. Introduction

The study of strokes in Africa bears at the same time an epidemiological, etiological, semiological and therapeutical interest. The studies made on the black continent [11] these early thirty years show the necessity in this sector which remains unexplored, to evaluate the incidence and the prevalence of stroke in order to elaborate programmes and research protocols adapted to our realities. However, it is difficult to have a coherent interpretation of the results of these studies because of the high variability of epidemiological clues.

In black Aflica, in Nigeria [1], the prevalence of strokes was 60,67/100.000 persons. These rates of prevalence observed in Africa go against the rate reported in industrialised countries 145/100.000 persons [2] and could suggest the existence of some particularities that are special to Africa continent.

In fact, since about fifty years, the study of population pyramid in black Africa showed a population with a high fecundity, with an important mortality and life expectancy relatively short (44-54 years) people under fifteen years represent 50-60% of the population. The demographic weigh of this group of age on the epidemiologic indices had been noticed by many showed that the strokes in black Africa went under a sharp decrease of mortality going from 70% to 18% [1], the progressivity of the handicap of the survived is unchanged. The thrombolysis is non-existent. Therefore according to the previsions of World Health Organisation (WHO) [4], black Africa is an epidemiologic and demographic transition phase with, in the year 2020, the standing back of infectious transmissible pathologies and the high increasing of non-infectious, non-transmissible pathologies. It is evident to think again about how to take care of strokes, in black Africa. Besides the difficulties to make an ultraprecious diagnostic of stokes which has to deal with an important lack of paraclinic means of explorations on the black continent, the care field organisation, reveals in most of these countries that to sharp delay (time between the admission of patient and the first care) is very high over 6 hours [1]. This explains itself with the non-availability of urgent drugs in drugstores of hospital fees being encharge of the patient. In the other respects, apart from the mastering of difficulties of the risk of classic cardio vascular factors (high blood pressure, diabetes, dyslipidemia, alcohol, tobacco …) many affections not yet controlled, endemic on the black continent, especially HIV, tuberculosis are those which give stroke in the field of cerebral vascularity [1]. Besides the genetic factors like CADASIL or the drepanocytose sickle cell, are not yet completely controlled [1]. In addition, the addiction to some drugs especially cannabis that can generate stroke in the field of reversible cerebral vasoconstriction, is not yet studied. At last the caring of ischemic stroke in sharp phase in the field of thrombolysis alerte allows to reduce even cancel the handicap for the patient. The cost of this therapeutic protocol remains high, 4000 to 5000 US dollars in 1996 [5]. It is understood that with the potential disengagement of African states from the health system of their countries, thrombolysis in case of ischemic stroke, especially in Togo where 57,4% of the population lives in extreme poverty [5] is an illusion.

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Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Pilot Study Revealed Association of DRD4 Promoter Variants with ADHD Associated Functional Deficit in Indian Probands

By Subhamita Maitra, Kaushik Mukherjee, Mahasweta Chatterjee, Arijit Karmakar, Swagata Sinha & Kanchan Mukhopadhyay

Manovikas Kendra

Abstract- *Background:* Attention Deficit Hyperactivity Disorder (ADHD) is often associated with cognitive deficit. Since brain regions regulating cognition has higher expression of Dopamine receptor 4 (DRD4), we explored association between functional DRD4 promoter variants and cognition of ADHD probands.

Methods: Subjects recruited following DSM-IV-TR were assessed for Short Attention Span (SAS) and Erratic Organization Capability (EOC), based on scores obtained through Conner's Parent Rating Scale and DSM-IV-TR as well as computerized games. Functional variants were analyzed in ADHD probands, their parents and age-matched controls.

Results: Probands exhibited significant impairment in SAS and EOC. rs10902180, rs747303, rs936462, showed association with cognitive deficit. Probands with co-morbid learning disability showed higher cognitive impairment. Significant interactive effects were evident between the markers.

Keywords: *ADHD; molecular genetics; cognitive impairment; learning difficulties.*

GJMR- A Classification: *NLMC Code: WL 348*

Strictly as per the compliance and regulations of:

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Subhamita Maitra [α], Kaushik Mukherjee [σ], Mahasweta Chatterjee [ρ], Arijit Karmakar [ω], Swagata Sinha [¥] & Kanchan Mukhopadhyay [§]

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Conclusion: Impaired in information processing and scholastic performance, strong genotype-phenotype correlations more robust in ADHD cases with learning difficulty, suggest significant contribution of DRD4 in ADHD etiology, possibly due to attenuated receptor functioning.

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I. Introduction

The current theory on Attention Deficit Hyperactivity Disorder (ADHD) emphasizes on delayed maturation of brain regions involved in controlling executive function (EF),[1,2] thus leading to age-inappropriate impulsivity, hyperactivity and inattention.[3] Though deficit in inhibitory control mechanisms was earlier hypothesized as the major cause for improper EF,[4] recent studies revealed that this is primarily moderated by deficits in basic information processing.[5] Apart from the core symptoms, individuals with ADHD frequently suffer from co-morbid learning difficulty (LD), oppositional defiant disorder, and conduct disorder,[3] which also could be due to improper information management.

Image analysis revealed significant reduction in the prefrontal cortex (PFC) volume of ADHD probands.[6] As PFC is interconnected with other brain regions like the neocortical regions, amygdala, limbic circuit and cerebellum, it was proposed to have vital role in memory encoding and retrieval as well as decision making,[7] emotion related arousal,[8] and motor movements.[9] PFC microcircuits are supposed to play key roles in perception of action cycle while dealing with different types of environmental and social stimuli thereby executing a particular behavioral response.[10] Thus sustained attention and information processing, mediators of executive processes, may also be regulated by PFC.

As proposed by Dr. Barkley, EF involves six sets of self regulatory activities, such as self-inhibition, self-directed sensory-motor action, self-directed private speech, self-directed emotion/motivation, self-directed play, and self-monitoring which eventually affect future consequences. [11] He also concluded that these six functions form the Instrumental-Self-directed level of EF that is most proximal to PFC development and functioning. Self inhibition, spatial management and sustenance of self-motivation form part of these self-regulatory behaviors and injuries / or developmental anomalies of the PFC were found to disturb these functions.

Dopamine (DA) is one of the major neurotransmitter involved in movement, motivation and other executive processes [12] and the PFC is enriched with DA receptors, both type I and II. While bioavailability of DA in the PFC and striatum is regulated by DA receptor 2 (DRD2), receptor 4 (DRD4) and DA transporter,[13] PFC is preferentially enriched with DRD4.[14] A dual role of DRD4 on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, hypothesized to underlie the mechanisms of evoke related response, inhibitory control and other cognitive processes, has also been documented; during the hyper-activated state of the PFC, DRD4 was found to reduce glutamatergic transmission while at the hypoactive state PFC was reported to trigger AMPA response via the same pathway.[15]

Genetic polymorphisms in the DRD4 have been explored widely. The most frequently investigated site is a variable number of tandem repeat in the exon3 and

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meta-analysis revealed association of higher repeats (>6R) with ADHD in the Caucasoid[16] as well as Indo-Caucasoid probands.[17] Individuals homozygous for the common 4R variant showed reduction in the PFC gray matter volume[18] while being less efficient in a measure of executive attention.[19] Based on these findings, we speculated that DRD4 may have a contributory role in the EF of ADHD probands and for the first time investigated association of functional DRD4 promoter variants with Erratic Organizational Capability (EOC) and Short Attention sustainability (SAS), as part of self-regulatory trajectories under EF, in eastern Indian probands with or without co-morbid LD.

II. Methods

a) Participants and study design

Nuclear families with ADHD probands (N=200; mean age 7.7 yrs; sex ratio M:F 9.5:1) were enrolled based on the Diagnostic and Statistical Manual for Mental Disorders-IV-text revised (DSM-IV-TR) criteria.[3] ADHD index, hyperactivity level and cognitive attributes/ inattentiveness of probands were measured by the Conners' Parent Rating Scale-Revised (CPRS).[20] Intelligence/developmental quotient were assessed by the Wechsler's Intelligence Scale for children[21] for proband above five years and Developmental Screening Test for children below 5 years.[22] Out of 200 probands, 160 were complete parent-proband trios, 22 had only one parent while 18 were affected probands only. Majority of the probands belonged to the combined subtype (72.5%) while hyperactive/impulsive (12.5%) and inattentive (15%) subtypes were only few. 60% probands showed cognitive deficit while 63% exhibited hyperactivity. Co-morbid conditions assessed using the DSM-IV-TR criteria[3] showed LD in 29% of probands. Subjects with only psychiatric problems including pervasive developmental disorders, any form of mental retardation (IQ ≤ 70) and fragile-X syndrome, were excluded.

Ethnically matched control subjects were evaluated for the DSM-IV-TR criteria for ADHD[3], hypothyroidism, intelligence/developmental quotient (>80) as well as for any psychiatric disorder running in the family and those without any abnormality (N=200; Mean age 13.45 yrs; sex ratio 1.4:1) were recruited. Informed written consent was obtained for participation in the study and the protocol was approved by the Institutional Human Ethics Committee.

b) Assessment of traits

SAS and EOC were measured through questions selected from the DSM-IV-TR and CPRS scale (Table 1), scores (0-3) were given based on the responses received, and the total score was converted to percentage. CPRS score percentage for each trait was cross validated with the DSM-IV-TR score and an individual exhibiting more than 5% deviation was excluded. Based on the CPRS score percentage, individuals having less than 30% were considered to have low deficit (1), whereas those with 30-60% were identified as having medium deficit (2) and more than 60% were coined as having maximum deficit (3).

Computerized games were used to measure the cognitive function of ADHD probands (N=25, 6-12 yrs, 23 male / 2 female) and controls (N=10, 7-12 yrs, 6 male / 4 female). Participants were tested for working memory (Game 1), speed (Game 2) and spatial (Game 3) information processing, , and dual N back test (Game 4) for 5 minutes. For each game, there were 3 levels with increasing complexity followed by automatic recording of score. Wrong entry in any round iterated the same level and thus score increased with delay/error in response.

Probands (N=80; mean age 12.67 ±3.95 years) were reassessed after 3 years using the same questionnaire (Table 1) to follow their performance.

c) Genetic analysis

Online programs F-SNP (compbio.cs.queensu.ca/F-SNP/), Brain-array (http://brainarray.mbni.med.umich.edu/brainarray/database/searchsnp/snpfunc.aspx), and SNPinfo (http://snpinfo.niehs.nih.gov/cgi-bin/snpinfo/snpfunc.cgi) were used to analyze functional roles of seven upstream variants. Peripheral blood leukocytes were processed for extraction of genomic DNA.[23] Oligonucleotides designed using the Primer3 (www.bioinformatics.nl/primer3plus/) program were used for PCR amplification in ABI Gene Amplifier #9700 PCR system. rs 916455 was genotyped by restriction fragment length polymorphism analysis of PCR amplicon using RsaI restriction enzyme (New England Biolab); in presence of the "T" allele, two fragments of 58 and 163 bp were generated. The other SNPs were analyzed by sequencing of the PCR amplicon in Applied Biosystems 3130 Genetic analyzer using Big Dye v 3.1 chemistry and Sequencing Analysis Software, v 5.2.

d) Data analysis

i. Association analysis

Unphased verion 3.1.7[24] was used for population- and family-based analysis. Hardy-Weinberg equilibrium (HWE) was analyzed using the online software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl-hwe) and Piface version 1.72[25] was used to quantify the strength of statistically significant results (P<=0.05). The Odd's ratio (OR) was calculated by online program (http://www.hutchon.net/ConfidOR.htm).

ii. Analysis of interaction between the sites

Interaction between haplotypes was analyzed by the Cocaphase program. Linkage Disequilibrium was calculated using the Haploview program.[26] SNP-SNP interaction was analyzed by the Multifactor dimensionality reduction (MDR) program. [27]

iii. *Genotype-phenotype correlation analysis*

Association between each phenotypic trait and the gene variants were analyzed by Mann-Whitney test (http://elegans.som.vcu.edu/~leon/stats/utest.html).

Association between genotypes and co-morbid LD was analyzed using the Cocaphase program.

ADHD probands were grouped into three categories, all cases, ADHD with co-morbid LD (ADHD+LD) and without LD (ADHD-LD) for analyzing the level of SAS and EOC. Frequency of probands having various levels of SAS and EOC, calculated through CPRS, were analyzed using the excel work book. Correlation between pair of traits was obtained through online Pearson's calculator (http://www.socscistatistics.com/tests/pearson/) and regression analysis software (http://www.alcula.com/calculators/statistics/linear-regression/) was used for calculating the interdependence of these traits.

iv. *Measurement of cognitive function*

Mean scores obtained for ADHD probands and controls through computerized assessment were analyzed by the 1 tailed unpaired T test using online software (http://studentsttest.com/).

III. Results

a) Analysis of variants

Sequence analysis showed presence of a novel G>T substitution (Table 2, NSNP) 45 bases before rs747302. All the seven SNPs are binding sites for transcription factors and four revealed moderate regulatory potential (Suppl Table S1). rs916455 is located in the CpG island (ratio=0.99).

Genotypes of rs747303 deviated from the HWE in the probands (P=0.0009). rs10902180 genotypes deviated for the proband (P=0.0001) as well their parents. Genotypes of all other variants followed the HWE. Population based analysis showed significant bias for rs10902180 "C" allele (Suppl Table S1; P=0.01, Power=71, OR=1.57) with a trend of association (P=0.08) for the "CC" genotype (Table 2). rs916455 "CC" and rs936462 "AA" genotypes showed significantly higher frequencies in the ADHD+LD probands as compared to control as well as ADHD-LD (Table 2, P<0.04). rs10902180 showed higher frequency of the "GG" genotype in the ADHD+LD compared to ADHD-LD individuals (P=0.001).

Family-based analysis revealed biased transmission of rs936462 "A", rs747303 "T", rs1800955 "T" and NSNP "G" alleles (Table 3). For rs1800955 "T", a paternal bias was noticed (χ^2= 6.32, P=0.01). Analysis of haplotypes failed to show any significant difference.

Linkage Disequilibrium pattern was different in the control individuals, probands and their parents, but coefficient of correlation was insignificant (Suppl Fig.1).

b) Analysis of phenotypic traits

EOC and SAS showed linear correlation in both ADHD-LD (R=0.73) and ADHD+LD (R=0.88). Regression analysis validated EOC score as a function of SAS for these subgroups (Y= 2.31+0.86X & y= 1.08X-10.30 respectively). Analysis between different subgroups exhibited higher number of ADHD+LD probands with high SAS score (χ^2=21; p>0.0001) as compared to ADHD-LD group (Suppl Fig. 2). No significant difference was noticed for the EOC score (Suppl Fig. 2). rs747303 "TT" showed association with higher EOC score (Suppl Table S2, P=0.05), while the NSNP "GG" showed association with both high EOC and SAS scores (P=0.02 & 0.04 respectively).

Performance of ADHD probands was poor, more strikingly for Game 1 and 2, as compared to age-matched control children (Fig. 1).

Association of higher scores for Game 1 and 2 with rs916455 "CC" was observed. rs936462 "AA" and rs747303 "TT" revealed nominal differences, while rs10902180 "GC" showed distinct difference in Game 2 score with a mild difference for Game 1 (Suppl Fig. 3). Higher mean score was also noticed for rs1800955 "CC" in case of Game4. No difference could be observed for rs747302 and data for NSNP could not be shown due to the presence of only one heterozygote (Suppl Fig. 3).

Interaction analysis revealed major independent effects of both SAS and EOC (Fig. 2 A & B respectively) in ADHD individuals exhibiting higher scores (score>1) against those having low score (score=1). With EOC as a phenotypic co-variate, interaction between rs916455-rs747302 and rs1800955-NSNP was also noticed (Fig. 2B). Stratification based on the presence of co-morbid LD revealed major independent effects of phenotypic traits and gene variants in ADHD-LD probands as compared to the control individuals (Fig. 2C), while in ADHD+LD individuals, strong interactive effect was observed between SAS–rs1800955 and EOC-rs747303 in absence of any major independent effect (Fig. 2 D), as compared to ADHD-LD individuals. Mild positive interaction was also noticed between SAS-rs747302, SAS-rs747303, and EOC-rs1800955 (Fig. 2D).

Follow up after three years showed that while the number of probands with high EOC gradually reduced with time (Suppl Fig. 4, Low T0/T3=2/24, High T0/T3= 44/15, χ2=32.5, P=0.0001), SAS score improved in a number of probands (Suppl Fig. 4, Low T0/T3= 0/11, High T0/T3= 56/48, χ2=11.5, P=0.003). ADHD subjects harboring rs916455CC, rs747303TT and NSNPGG genotypes had higher EOC scores after three years, while NSNP also showed association with high EOC score (Suppl Table S3). Follow up study also revealed strikingly low scholastic improvement in ADHD+LD (58%) probands as compared to ADHD-LD (79%).

IV. Discussion

Earlier investigators reported delayed maturation of brain regions controlling EF, affecting self regulation, attention and working memory.[2] Since these regions are enriched with DRD4 receptor, we investigated association between DRD4 promoter variants and EF of ADHD probands. LD is a major co-morbid condition and may result from low attention sustainability, memory retrieval, working memory, and poor comprehension. We compared the genotypic pattern of ADHD+LD individuals with that of ADHD-LD individuals as well as controls to find out if any particular genotype is affecting the trait.

Based on the data obtained, we for the first time report significant association of DRD4 promoter variants with EF deficit of Indo-Caucasoid ADHD probands. F-SNP analysis revealed that rs9164555, an upstream variant, may regulate binding of transcription factor, though the mechanism is yet to be understood. The rs916455 "C" allele showed association with persistence of symptoms in Chinese ADHD subjects.[28] Follow up of ADHD probands during the present study also revealed association of "CC" with high EOC score. Higher occurrence of the "CC" genotype was earlier reported in ADHD+LD probands[29] and further analysis in extended samples also revealed association of the "CC" genotype with ADHD+LD as compared to controls (P=0.05) as well as ADHD-LD (P=0.04). MDR analysis exhibited additive effect of rs916455 and rs747302 on EOC. In ADHD+LD individuals, this site showed strong independent effect. "CC" was also associated with Game 1 and 2, depicting its role in working memory impairment as well as poor cognitive flexibility while follow up revealed link between the "CC" genotype and poor attention.

rs747302, presented as a trimorphic variant (C/A/G) in the dbSNP database (build 86/142), showed only two alleles (C/G) in the present study as well as previous investigations.[30, 31] F-SNP analysis suggested that the C allele affects binding of transcription factor E2F. Comparative analysis failed to show any significant association of rs747302 with ADHD in the Indo-Caucasoid population and further investigation in other ethnic population is warranted to understand the actual role.

Frequency of rs936462 "A" allele was 50% less in the studied Indo-Caucasoid population as compared to the Hungarian population.[31] We have noticed preferential transmission of the "A" allele by family-based analysis (Odds ratio 4.73). Individuals harboring "AA" showed higher score for Game 1, 3 and 4. While Game 1 is a test for working memory, Game 3 and 4 requires sustained attention and organizational efficiency. Therefore, the "A" allele may be considered as a risk allele in this population. A previous report showed that absence of the "G" allele caused a significant difference in the genotype of -521 C/T, i.e. rs1800955,[31] though in the studied Indian population no such difference was noticed. On the basis of the present study, rs936462 merits further analysis to understand the role of the site in the disease etiology.

rs747303 was rarely investigated in ADHD patients and the present study revealed biased transmission of the "T" allele (OR 2.81). F-SNP analyses suggested regulation of transcriptional activity; the GC box disappears in presence of the T allele thus affecting transcription initiation. ADHD probands with the "TT" genotype had poorer information processing capability as compared to probands harboring the "GG" genotype. This is also indicated by scores for Game 3 & 4. MDR analysis showed positive effect of this site on poor attention span in ADHD+LD subjects. On the basis of these findings, rs747303 "T" allele could be considered as a risk variant for ADHD which merits further in depth analysis.

This first association analysis on rs10902180 identified the site as a transcriptional regulator. Marginally higher frequency of the "C" allele and "CC" genotype was noticed in the ADHD probands as compared to control. Individuals with the "CC" genotype obtained higher scores for Game 1 and 2. On the other hand, analysis among the subgroups showed significantly higher frequency of the "GG" genotype in ADHD+LD. This contradictory finding may suggest a different mechanism of DRD4 expression in the ADHD+LD subgroup since the gene not only interferes with NMDA receptor or other D2 type receptors, but also interacts with D1 type D5 receptors which work by upstream regulation of gene (analyzed by KEGG pathway). MDR analysis showed strong independent effect of this site on the phenotypic traits. Since our study involves only limited number of ADHD+LD probands, we conclude that this site may have a role in the learning problem of ADHD probands which merits further analysis in higher number of subjects.

rs1800955 is a transcriptional regulator widely investigated in ADHD as well as other psychiatric disorders.[32] Transcription factor CAP is functional in presence of the "T" allele; transcriptional activity was reduced by 40% in presence of the "T" allele[33] though the finding could not be reproduced.[34] Earlier studies on the Indo-Caucasoid population revealed biased parental transmission of haplotype 7R-T of DRD4 Exon3 VNTR and rs1800955.[35] The present study also revealed parental over transmission of "T" to the probands, which is basically paternal in nature. "CC" was associated with higher scores for SAS and EOC measured through CRS as well as Game 2 and 4 suggesting its role in cognitive impairment as a whole. MDR showed strong independent effect of rs1800955 in ADHD. In ADHD+LD both attention sustainability and information processing was found to be affected in presence of this variant

thereby suggesting a role of this site in ADHD associated cognitive deficit.

The novel substitution NSNP detected in the 5' upstream region showed a parental bias in transmission of the wild type allele and interaction with rs1800955. The heterozygous form showed association with both SAS and EOC. However the site failed to show any significant functional contribution thus making it difficult to interpret its role.

Linkage Disequilibrium between rs747302–rs1800955 and rs916455–rs1800955 in the Indo-Caucasoid control population was similar to that observed in the Japanese population.[36] However, in the Hungarian population, a strong bond was noticed between rs936462-rs1800955[30] which was absent in the Indian population. Further, in families with ADHD probands, the pattern was totally different as compared to the ethnically matched control population. From the observed pattern, we may interpret that the DRD4 promoter region harbors recombination hotspots which culminates in a break in the Indo-Caucasoid population.

ADHD associated EF deficit was hypothesized to occur from poor flexibility, self motivation and working memory, ultimately giving rise to altered behavioral response.[11,37] Uncontrolled inhibition with triggered impulsivity and error prone behavior was also noticed.[37] Further investigation showed improper information processing as the major reason for ADHD associated symptoms.[5] These domains are supposed to be affected in children with LD too. As In the present study, we have noticed aberrant information processing along with short attention sustainability. Higher scores for Game 1 and 2 in ADHD probands indicate poor working memory and cognitive flexibility as a result of improper information processing. Scores for Game 3 and 4 were moderately high in the ADHD probands as well as healthy individuals which may indicate that these traits involve a more complicated network of information processing which develops during adolescence. MDR analysis also revealed strong major effects of these two phenotypic traits in addition to independent effect of the studied sites and an additive effect of rs916455-rs747302 on EOC. Comparative analysis between subgroups showed that phenotypic traits of ADHD+LD subjects are affected more severely by interactive effect of the markers; while in ADHD-LD both SAS and EOC showed strong independent effects, interactive affects were pronounced in ADHD+LD. Follow up revealed a constant deficit in attention sustainability with a gradual improvement in EOC and academic achievement was worse for ADHD+LD patients. rs916455 "CC", rs747302CC, rs936462 "AA", rs747303 "TT", rs1800955 "CT/TT" and NSNP "GG" were found to be more frequent in subjects with high and medium score for SAS and EOC indicating significant impact of these genotypes in the cognitive function. Follow up study also confirmed role of rs747303 "TT", rs1800955 "TT" and NSNP "GG" in ADHD.

Since ADHD probands are believed to have an altered function of the frontal lobe[38] and DRD4 density is high in this region, we speculated that the promoter variants may alter transcriptional activity leading to a reduction in DRD4 receptor density, thereby causing altered behavioral and cognitive outcome. The data obtained indicate that failure in information processing, leading to reduction in attention span, may lead to the symptoms of ADHD which is more evident in subjects with co-morbid LD. Further analysis involving additional functional variants is warranted in large cohort of subjects to validate our observation.

Acknowledgement

This work was sponsored by the Department of Science & Technology, Govt. of India (SR/CSI/17/2009), SM was a DST project fellow. Authors are thankful to the study volunteers for participation.

Authors' contribution

Subhamita Maitra performed genotyping and statistical analysis, participated in examination of cognitive function and prepared the manuscript draft. Kaushik Mukherjee helped in the assessment of cognitive function. Mahasweta Chatteree and Arijit Karmakar performed genotyping. Swagata Sinha recruited the study subjects and helped in functional assessment. Kanchan Mukhopadhyay designed the study, assessed cognitive function, monitored the development, and edited the manuscript draft. All the authors approved the final version of the Manuscript.

Declaration of conflicting interests

Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abbreviations: ADHD- Attention deficit hyperactivity disorder; AMPA- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CRS- Conners' rating scale; DA-Dopamine; DRD2-Dopamine D2 receptor; DRD4-Dopamine D4 receptor; DSM-IV-TR-Diagnostic and Statistical Manual for Mental Disorders-4th edition-text revised; EOC-Erratic organization capability; HWE-Hardy-Weinberg equilibrium; LD-Learning disability; MDR-Multifactor dimension reduction test; NMDA-N methyl D aspartate; OR-Odds ratio; PFC-Prefrontal cortex; SAS-Short attention sustainability; SNP-Single nucleotide polymorphism.

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Legend to Figures

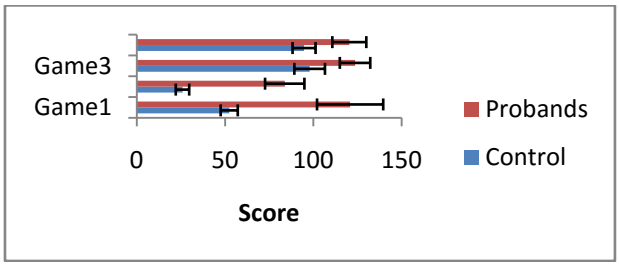


Figure 1: Comparative analysis between control individuals and ADHD probands for mean scores obtained through computerized games.

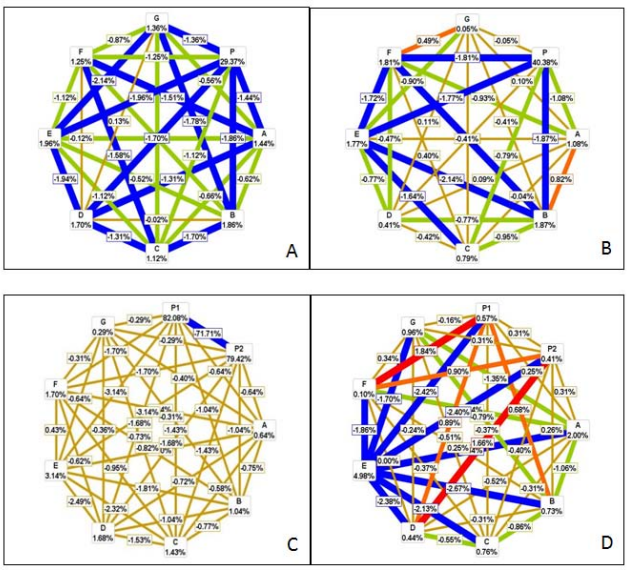


Figure 2: MDR analysis performed using case-control data: (A) EOC & (B) SAS as phenotypic co-variates; (C) ADHD-LD and (D) ADHD+LD subgroups. P1-SAS, P2-EOC, A-rs916455, B-rs747302, C-rs936462, D-rs747303, E-rs10902180, F-1800955, G-NSNP.

Table 1 : Assessment of SAS and EOC from questions selected from DSM-IV and CRS.

Scales used for analysis	SAS	EOC
DSM IV-TR	Make careless mistakes in school/work/ other activities	Does not follow instruction/fails to finish school work
	Has difficulty in sustained attention	Has difficulty in organizing task
	Lacks attention during one/one conversation	Often looses things necessary for tasks and activities
	Is often easily distracted by extraneous stimuli	Is often forgetful in daily activities
	Reluctant to perform tasks requiring mental effort	Reluctant to perform tasks that require mental effort
CRS	Inattentive, easily distracted	Has difficulty doing or completing home work
	Short attention span	Messy or disorganized at home or school
	Distractibility or attention span a problem	Needs close supervision to get through assignments
	Gets distracted when given instruction to do something	Avoids or expresses reluctance in tasks requiring sustained mental effort
	Has trouble concentrating in class	Does not follow through instructions and fails to finish school works.
	Easily frustrated in efforts	
	Avoids or expresses reluctance in tasks that require sustained mental effort	

Table 2 : Comparative analysis on genotypic frequencies of DRD4 promoter variants.

*Compared to controls; ! Compared to ADHD-LD.

ID	Genotype	Control (N=200)	All (N=200)	χ^2(P)	Probands		χ^2 (P)*	χ^2 (P)!
					ADHD-LD (N=146)	ADHD+LD (N=54)		
rs916455	CC	0.88	0.89	1.53	0.85	0.94	6.34	6.34
	CT	0.12	0.10	(0.47)	0.14	0.04	(0.05)	(0.04)
	TT	0.0	0.01		0.01	0.02		
rs747302	CC	0.34	0.39	0.95	0.37	0.41	1.22	1.82
	GC	0.46	0.43	(0.62)	0.46	0.37	(0.54)	(0.40)
	GG	0.20	0.18		0.17	0.22		
	AA	0.90	0.93	3.22	0.91	1.0	7.43	9.42
rs936462	GA	0.09	0.07	(0.20)	0.09	0.0	(0.02)	(0.002)
	GG	0.01	0.0		0.0	0.0		
rs747303	GG	0.09	0.10	3.97	0.10	0.12	4.44	1.79
	GT	0.36	0.26	(0.14)	0.28	0.20	(0.10)	(0.41)
	TT	0.55	0.64		0.62	0.68		
	GG	0.77	0.66	5.02	0.61	0.83	1.06	13.2
rs10902180	GC	0.17	0.24	(0.08)	0.26	0.14	(0.59)	(0.001)
	CC	0.06	0.10		0.13	0.03		
rs1800955	CC	0.19	0.16	0.93	0.16	0.15	2.08	0.78
	CT	0.51	0.50	(0.62)	0.49	0.44	(0.35)	(0.68)
	TT	0.30	0.34		0.35	0.41		
NSNP	GG	0.82	0.80	0.10	0.81	0.77	0.47	0.48
	GT	0.18	0.20	(0.74)	0.19	0.23	(0.49)	(0.49)
	TT	0.0	0.0		0.00	0.00		

Table 3 : Analysis of familial allelic transmission by Haplotype-based Haplotype Relative Risk test.

SNP	Allele	Transmitted	Not transmitted	χ^2(P)	Power (%)	Odds Ratio
rs916455	C	0.96	0.94	1.47	---	---
	T	0.04	0.06	(0.23)		
rs747302	C	0.63	0.59	0.64	---	---
	G	0.37	0.41	(0.42)		
rs936462	A	0.99	0.93	9.01	85	4.73
	G	0.01	0.07	(0.003)		(1.15- 19.41)
rs747303	G	0.10	0.25	17.7	99	2.81
	T	0.90	0.75	(2.59e-005)		(1.36-5.82)
rs10902180	G	0.83	0.82	0.07	---	---
	C	0.17	0.18	(0.79)		
rs1800955	C	0.37	0.48	5.54	65	1.52
	T	0.63	0.52	(0.02)		(0.89-2.74)
NSNP	G	0.97	0.82	27.15	99	4.89
	T	0.03	0.18	(1.89e-007)		(1.94 -12.06)

N.B. Statistically significant differences are presented in bold.

Supplementary Table S1 : Details on studied DRD4 promoter variants.

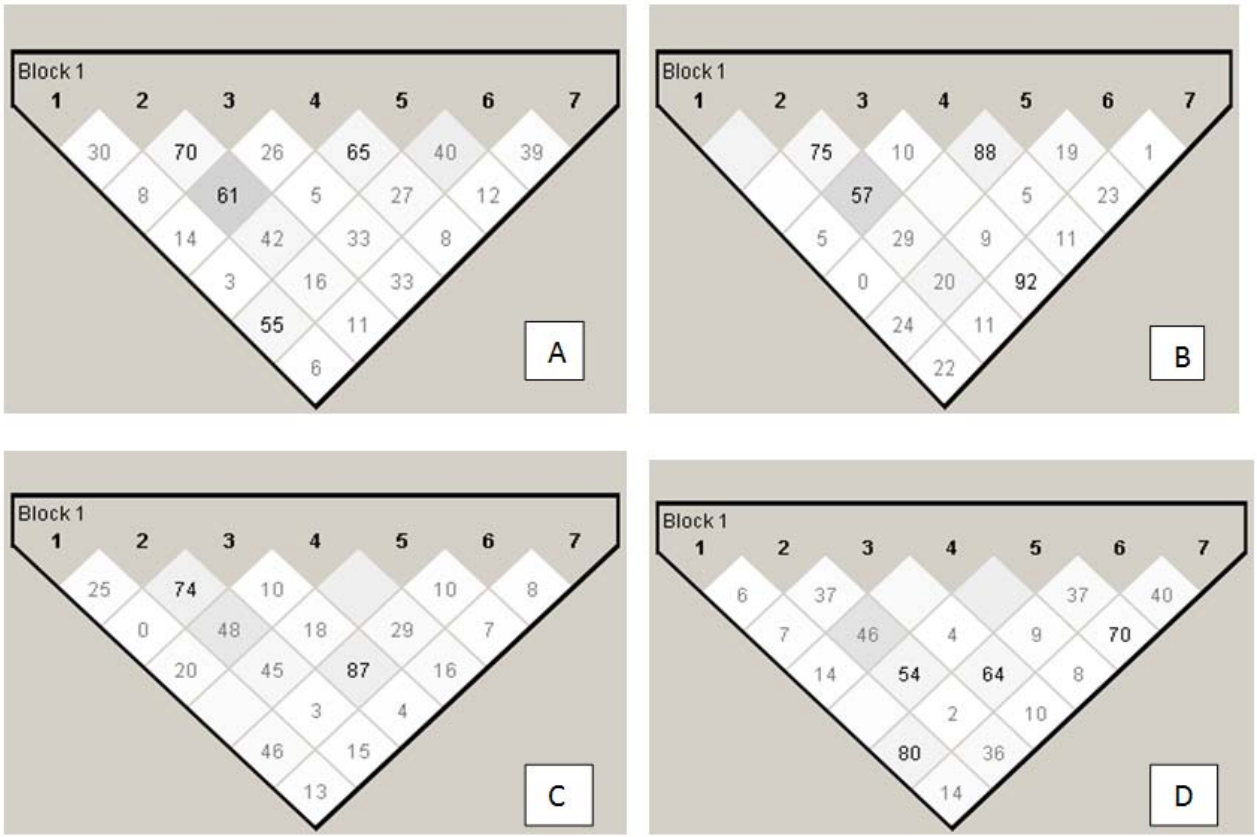
ID	Predicted functional score		Allele	Frequency		χ^2(P)
	F-SNP	SNPinfo		Control	Probands	
rs916455	0.109	0.148029	C	0.942	0.941	0.0002
			T	0.057	0.058	(0.96)
rs747302	0.208	0.086621	C	0.58	0.61	0.78
			G	0.42	0.39	(0.37)
rs936462	0	0.086409	A	0.95	0.97	1.62
			G	0.05	0.03	(0.20)
rs747303	0.208	0.172765	G	0.27	0.23	1.67
			T	0.73	0.77	(0.20)
rs10902180	0.05	0.163562	G	0.86	0.78	6.39
			C	0.14	0.20	(0.01)
rs1800955	0.176	0.181188	C	0.45	0.41	0.91
			T	0.55	0.59	(0.34)
NSNP	None detected	--	G	0.91	0.90	1.00
			T	0.09	0.10	(0.75)

Supplementary Table S2 : Analysis of association between genotypes and phenotypic attributes of ADHD probands

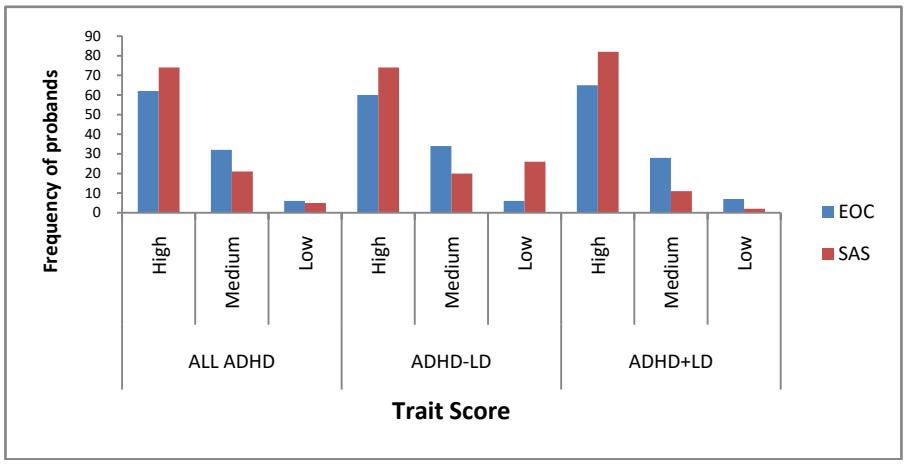
ID	Genotype	EOC		SAS	
		Mean± SE	P value	Mean± SE	P value
rs916455	CC	65.38 2.06	--	70.51,1.66	--
	CT	65.19 5.34		71.82, 3.96	
rs747302	CC	66.72 3.13		74.37,2.24	--
	GC	66.41 2.77	--	68.04, 2.61	
	GG	60.99 5.08		71.05, 3.79	
rs936462	AA	65.17 2.02	--	71.17,1.66	--
	GA	69.67 6.96		67.60, 6.31	
rs747303	GG	58.78±4.43	--	71.71±4.44	---
	GT	64.90±3.90		70.06,3.35	
	TT	67.10±2.53	0.05	71.59±1.99	
rs10902180	GG	67.21±2.20	--	70.21,1.89	--
	GC	61.91± 4.83		73.68,3.91	
	CC	61.46±6.51		72.67,4.39	
rs1800955	TT	68.40±3.11	0.09	72.7±2.75	--
	CT	62.51±2.73		69.31±2.19	
	CC	69.30±5.21	--	74.68,4.13	
NSNP	GG	67.48±2.15	0.02	72.37±1.81	0.04
	GT	56.92±4.78		64.67±4.01	

Supplementary Table S3 : Genotype-phenotype association of probands obtained after follow up.

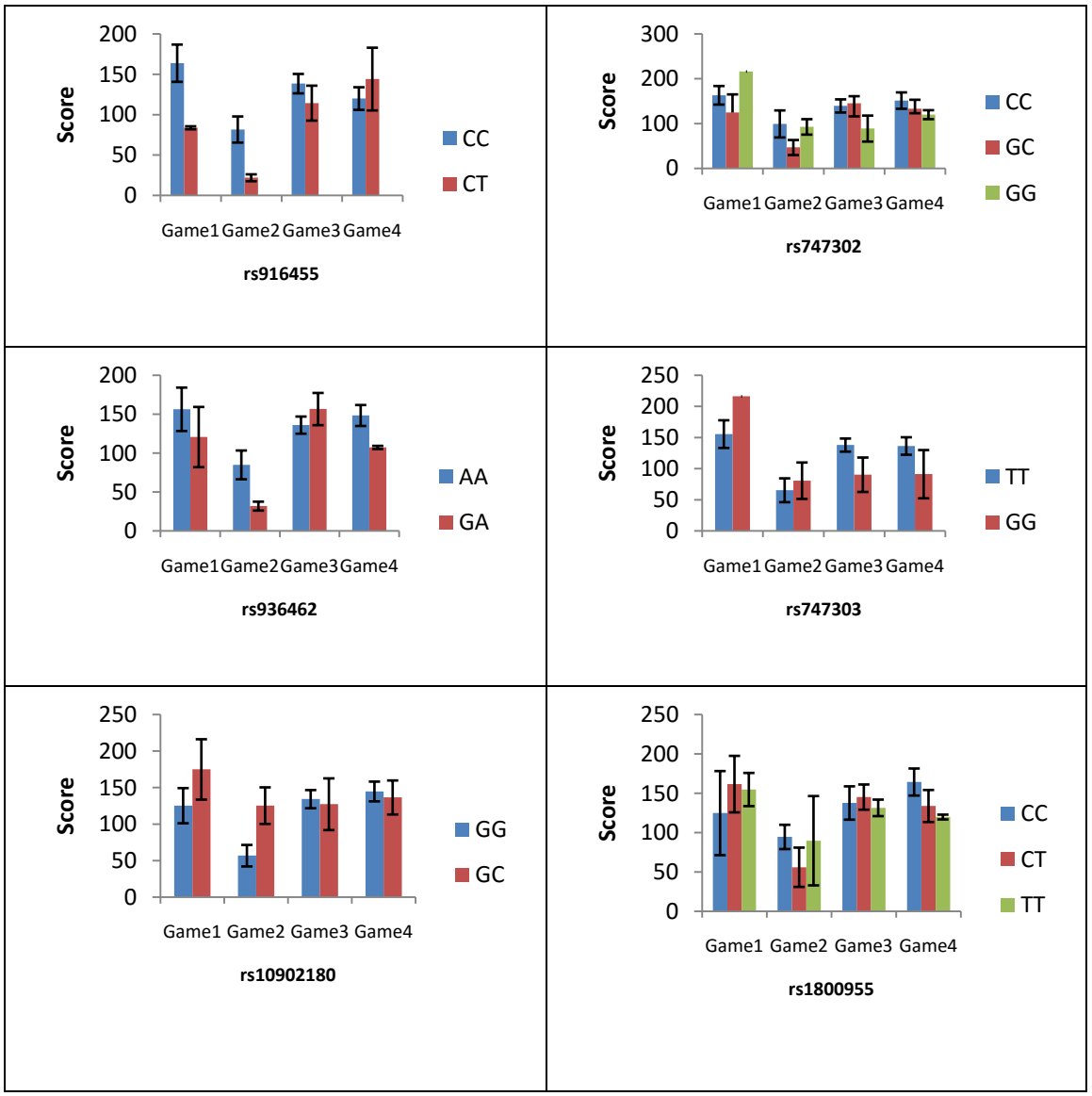
Score for phenotypic traits							
ID	Genotypes	SAS				EOC	
		Low	Medium	High	Low	Medium	High
rs916455	CC	100	100	92	90	93	100
	CT	0	0	8	10	7	0
rs747302	CC	13	64	46	32	52	64
	GC	62	29	36	50	28	36
	GG	25	7	18	18	20	0
rs936462	AA	89	100	93	91	96	93
	GA	11	0	7	9	4	7
rs747303	GG	22	0	7	14	4	7
	GT	22	8	28	36	17	14
	TT	56	92	65	50	79	79
rs10902180	GG	78	50	77	73	74	79
	GC	22	29	14	23	10	7
	CC	0	21	9	4	16	14
rs1800955	CC	12	7	12	10	16	7
	CT	44	57	49	45	26	57
	TT	44	36	39	45	26	57
NSNP	GG	63	83	74	63	82	77
	GT	37	17	26	37	18	23



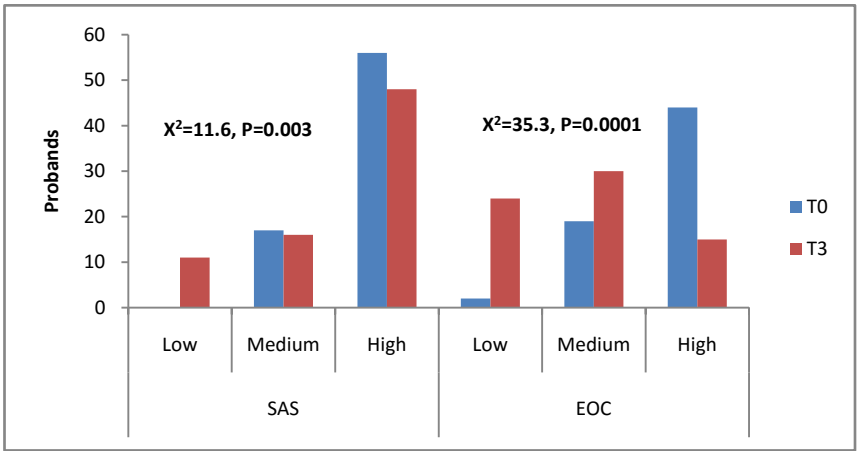
Supplementary Figure 1 : LD analysis for all ADHD probands (A), Father of the probands (B), Mother of the probands (C), ethnically matched healthy individuals (D).



Supplementary Figure 2 : Comparative analysis subgroups of ADHD individuals having different levels of EOC & SAS scores obtained from CPRS.



Supplementary Figure 3 : Analysis of performance of ADHD probands based on their genotypic constitution.



Supplementary Figure 4 : Frequency of probands with different levels of trait score at the time of recruitment (T0) and after three years (T3).

Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Recurring Ischemic Infarcts Showing Biermer's Disease Associeted with Protein S Deficiency

By Kokou Mensah Guinhouya, Léhleng Agba, Nyinévi Anayo & Mofou Belo

Universite de Lome

Observation- Mrs ASS….AKOU, 36 married and right handed household was at her second episode of stroke in six months.

Concerning her history; six months ago, during her first episode of stroke she was discovered and known to have a high blood pressure in the left anterior cerebral artery, responsible of an after effects right crural hemiparesis at 4/5.

She was not using hormonal contraception and there was not a sign of alcoholic or tobacco intoxication. Since six months she has been under second prevention with acetylsalicylic under 100 mg per day and sartan 150 mg per day.

The current episode was marked by a brutal installation of a left hemi body deficit predominant to inferior member in the morning of 26th December 2014 at her home. When she was admitted the exam allowed to note a blood pressure of 160/80 Hg in the left hand and 160/90 mmHg in the right, a beat of 78 pulsations per minute, a temperature at 37°4C talking of a neurology she was conscious without trouble of superior functions.

GJMR- A Classification: NLMC Code: WL 348

RECURRINGISCHEMICINFARCTSSHOWINGBIERMERSDISEASEASSOCIETEDWITHPROTEINSDEFICIENCY

Strictly as per the compliance and regulations of:

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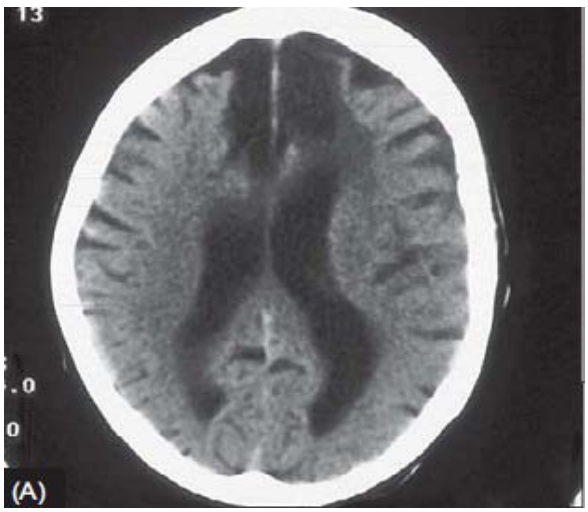

Figure 1 : Infarcts in both left and right anterior cerebral arteries

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Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Size of Hemorrhage on CT Scan and GC Scale use to Determine the Outcome of Hemorrhagic Stroke in Hypertensive Patients

By Milisha Lal, Nisha Gaur, Sumit Kamble, Harsh Chapadia, Sindhu Avula, Karthik Gangu, Kimmyben Patel & Abhishek Vadher

North Shore University hospital, United States

Abstract- *Introduction:* This study was to identify hypertensive Intracranial Hemorrhage with hematoma as well as the relation to various factors and outcomes.

Objective: To find the correlation between the site and size of hemorrhage, GCS score, and the outcome.

Methods: This is a prospective observational trial. The study consists of 65 patients with Intracranial hemorrhage, presenting with the criteria and symptoms in order to correlate with the GCS score and GC scale. This study was conducted at Shree Sayaji General Hospital, Baroda during December 2013 to November 2014. The GC scale was used to assess the outcome. The GC score was used for distribution of the patients with presenting symptoms. CT scan of the head was also used to identify the site of the hemorrhage and the size of the hemorrhage.

Results: The increase in hematoma volume in the study shows the high percentage of mortality. This shows that the lower the GC score is worse for prognosis than a higher GC score of >14.

Conclusion: Our results show that a low GC score and high size of the bleed can significantly affect the prognosis.

GJMR- A Classification: *NLMC Code: WG 106, WH 312*

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Milisha Lal [α], Nisha Gaur [σ], Sumit Kamble [ρ], Harsh Chapadia [ω], Sindhu Avula [¥], Karthik Gangu [§], Kimmyben Patel [χ] & Abhishek Vadher [ν]

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I. Introduction

Cerebrovascular accident or stroke is defined as an acute loss of focal and at times global (applied to patient in deep coma and those with subarachnoid hemorrhage) cerebral function, the symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin(WHO). Stroke can be ischemic or hemorrhagic and this is due to lack of blood flow to the brain and bleeding in the brain tissue respectively. Stroke can manifest with symptoms like loss of sensory or motor functions on one side of the body. It can also manifest as loss of vision, inability to speak or understand[1,2]. Cerebrovascular accidents represent third commonest cause of death worldwide. In United States, every year around 795000 people suffer from stroke and 130000 people die from stroke which is equal to 1 in every 20 deaths[3]. 87% of the stroke are due to ischemia and the rest 13% are due to hemorrhage[4]. The death due to stroke annually in United States is 130000 which is equal to 1 in every 20. Hypertension is the most important risk factor for stroke[5]. Hemorrhagic stroke has higher morbidity and mortality when compared to ischemic stroke. Hemorrhagic stroke is due to bleeding either in the brain or in the subarachnoid space[6]. Identifying high risk patients for development of Intracerebral Hemorrhage and to institute vigorous treatment in these patients is vital for prevention of Intracerebral Hemorrhage. Factors such as age, the score on Glasgow coma scale, the size of hematoma, rupture of hemorrhage in ventricle, midline shift and pulse pressure have been identified as determinant of outcome. The clinical and the CT correlates may contribute to the ultimate prognosis of these patients. By studying prognostic parameters of hypertensive Intracerebral Hemorrhage we can identify high risk patients, who are prone to develop Intracerebral Hemorrhage. Therefore, we can offer prompt and right treatment to patients with Intracerebral Hemorrhage.

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II. Objectives

1. To study the prognosis of patients with hypertensive intracerebral hemorrhage clinically.
2. To study prognosis of patients of hypertensive intracerebral hemorrhage with help of CT scan brain.

III. Materials and Methods

This is a prospective observational study with 65 patients. Follow up was done after one month of the patients included in the study. All CT proven hypertensive intracerebral haemorrhage patients admitted included in study with systolic BP >140mm of Hg and diastolic BP >90 mm of Hg. Patients having haemorrhage as a result of head injury, bleed in primary or secondary brain tumours, haemorrhage within a cerebral infarct, bleeding secondary to arteriovenous malformation and aneurysms were excluded. A thorough General examination was undertaken in particular for Glasgow coma scale, Vital examination

including temperature, pulse, respiratory rate, and blood pressure was noted, Peripheral signs of atherosclerosis like arcus senillis, locomotor, brachialis, thickened vessel wall, vascular bruit, xanthomas and xanthelesmas. Detailed Nervous System examination was doneincluding fundoscopy. After history and examination investigations like Complete blood count, Urine albumin, sugar, urine microscopy, Random blood sugar on admission, Serum urea, creatinine levels as renal function test, Lipid Profile: total cholesterol, Triglyseride, LDL level, HDL Level, VLDL, total cholesterol/HDL ratio, LDL/HDL ratio were done. ECG to find out if signs of ischemia, arrhythmia, hypertrophy are present or not. In CT scan a preliminary lateral topogram of the cranium was obtained. Serial transaxial scans were then performed with OM line as reference and employing 10mm and 5 mm sections. 5/5 mm sections were performed through posterior fossa. CT Head was carried out to know the site, size, volume, mass effect, ventricular extension, cerebral edema of intracerebral hemorrhage. All data was analysed using appropriate statistical tests. A p value of $<.05$ will be considered significant. Data was entered in excel sheet and analyzed by EPI INFO software.

IV. Result and Analysis

Table -1 : Age Distribution of Hypertensive Intracerebral Hemorrhage In Study

Age group (yrs)	Survived	Expired	Total
30-39	2	0	2
40-49	5	2	7
50-59	5	6	11
60-69	6	15	21
70-79	4	9	13
80-89	2	6	8
>90	0	3	3
Total	24	41	65

Two thirds of the stroke are in patients with age greater than 65[7]. In our study, there were 45 patients with age > 60 which is 69.23%.

Table-2 : Distribution According To Presenting Symptoms

Symptoms	No.of cases	Percentage
Weakness of limb		
- Hemiplegia	41	46.15%
- single limb	2	3.0%
Altered sensorium	40	61.5%
Headache	31	47.69%
Vomiting	31	47.69%
Convulsion	7	10.76%
Sensory symptoms	-	-
Vertigo	2	3.0%
Aphasia	1	1.5%

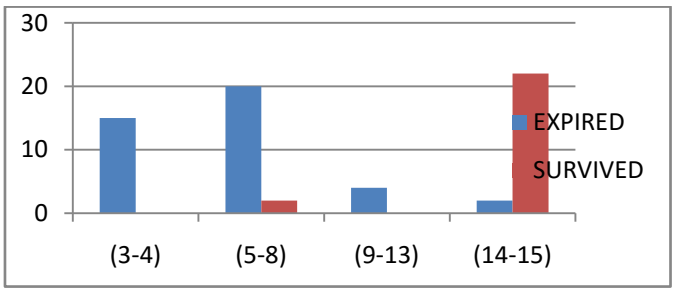
Maximum patients presented with altered sensorium (61.5%). Headache was present in 47.69% patients and vomiting was present in 47.69%. Hemiplegia was present in 46.1% patients.

In our study 40 (61.5%) patients were known case of hypertension, in which 22 (55%) patients expired. Our study is showing higher mortality (76%) in first time diagnosed hypertensive patients than in patients who were known case of hypertension.

In our study 14 (21.5%) patients were known case of Diabetes in which 12 (85.7%) patients expired. So higher mortality was seen in patients with Diabetes Mellitus (85.7%) than in patients without Diabetes (56.8%). In our study 37(56.9%) were smokers and higher mortality (70.2%) was seen amongst smokers than nonsmokers(53.6%).

Table-3 : Distribution of Patients With Gc Score and Correlation with Outcome

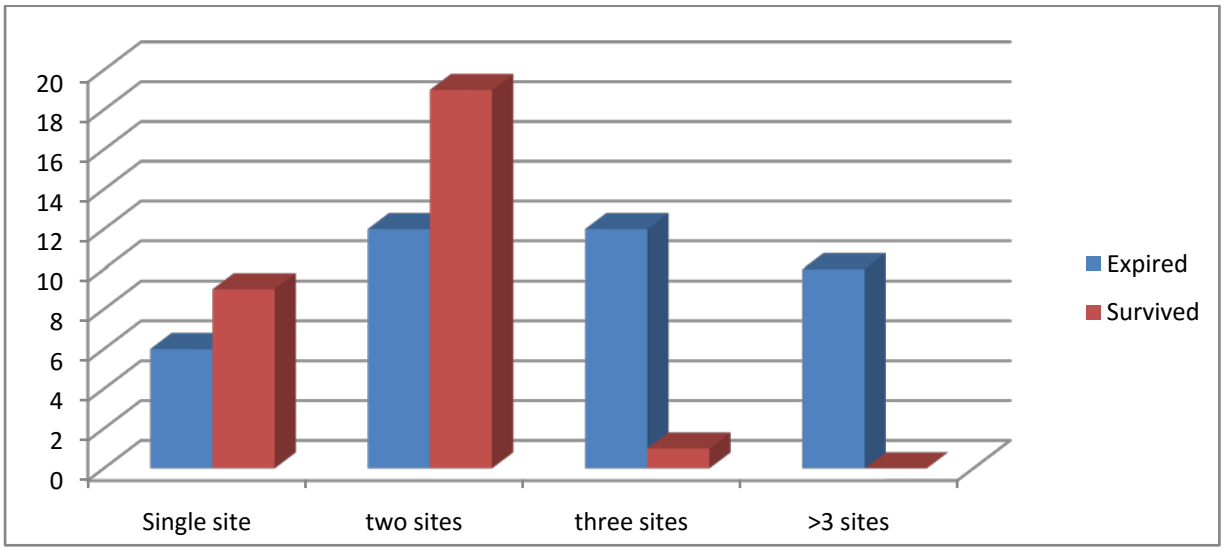
GC Score	Total Cases	Survived (%)	Expired (%)	P value
3-4	15(23.1%)	-	15 (100%)	0.002
5-8	22(33.8%)	2(9.1%)	20 (90.90%)	
9-13	4(6.1%)	-	4 (100%)	
14-15	24(36.9%)	22(91.7%)	2 (8.3%)	
TOTAL	65	24(36.9%)	41 (63.1%)	



In our study maximum patients were in GC score 14-15 (53.3%). GC Score 3-4, 5-8, 9-13 had 100%, 90.9%, 100% mortality respectively, but GC Score 14-15 had only 8.5% mortality. This shows that prognosis (mortality) is worse with lower GC Score (p value = 0.002). This is statistically significant.

Table-4: Correlation between Site of Hemorrhage, Gcs Score and Outcome

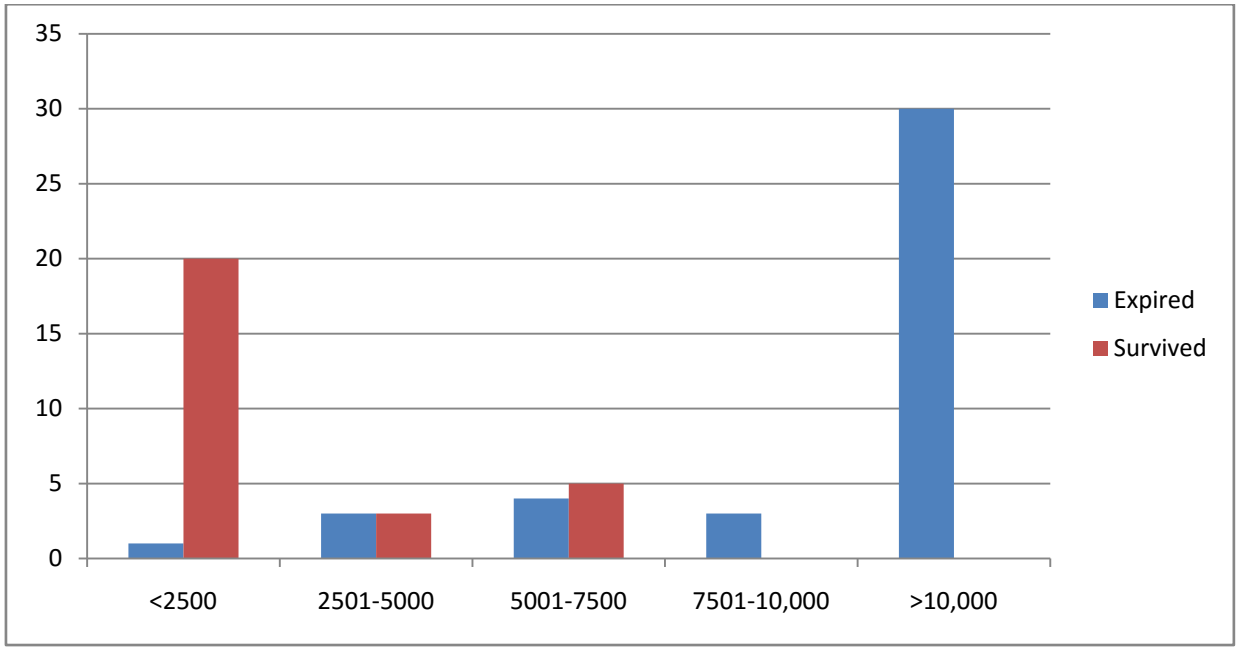
Site of Hemorrhage	NO. of PT	GCS Score				Expired
Single site of hemorrhage:		3-4	5-8	9-13	14-15	
• Cerebral cortex	5	-	2	-	3	2(40%)
• Thalamus	2	-	1	-	1	1(50%)
• Internal capsule	-	-	-	-	-	
• Putamen	-	-	-	-	-	
• Basal ganglion	2	-	-	-	2	1(50%)
• Cerebellum	4	1	2	-	1	2(50%)
Total patients	13(20%)	1(7.7%)	5(38.4)	-	7(53.8%)	6(46.2%)
Two site of hemorrhage:						
• Fronto-temporal	5		2		1	2(40%)
• Temporo-parietal	2		2			2(100%)
• Frontal-parietal	3	2	1			3(100%)
• Thalamus+internal capsule	15		2	1	12	3
• Basal ganglia+internal capsule	5	1				1
• Pons+mid brain	1	1	1		3	1
Total	31(47.7%)	4(12.9%)	8(25.8%)	1(3.2%)	16(51.6%)	13(18.46%)
Three site of hemorrhage:						
• Thalamus-basal ganglia-internal capsule	3	1	2			3
• Frontal-parieto-temporal	6	4	1	1		5
• Frontal+thalamus+internal capsule	1	1				1
• Basal ganglia+thalamus+midbrain	3	3				3
Total	13(20%)	9(69.2%)	3(23%)	1(7.6%)		12(92.3%)
>3 sites of hemorrhage	10(15.4%)	3(30%)	6(60%)	1(10%)		10(100%)



In our study patients with single site hemorrhage were 13(20%) with 46.2% mortality, 46.6% with GC score of 14-15 at the time of presentation. With three sites of hemorrhage 69.2 % patients were in GC score 3-4 and 92.3 % patients expired. With > 3 sites there was 100% mortality. So in our study with increasing sites of hemorrhage there is decreasing GC score at presentation with increasing mortality trend (p value= 0.07). Here, as p value is >0.05, this is not statistically significant. But as per some studies, brain stem hematoma, intraventricular extension of bleed and ventricular compression along and with midline shift are associated with early mortality in intracranial hemorrhage[8].

Table-5: Size of Hemorrhage Versus Outcome

Volume of Hemorrhage(mm3)	NO. Of Cases	NO. Of Patients Expired(%)	P value
<2500	21(32.3%)	1(4.1%)	0.0001
2501-5000	6(9.2%)	3(50%)	
5001-7500	5(7.6%)	4(80%)	
7501-10000	3(4.6%)	3(100%)	
>10000	30(46.15%)	30(100%)	



In our study maximum no. of patients had hematoma volume >10,000 mm3 - 30(46.15%) followed by 21 (32.3%) patients with volume <2500 mm3 .Mortality is rising with increasing volume of hemorrhage in the study. There was 100% mortality with hematoma volume >7500mm3. P value was 0.0001 and this shows that the result was statistically significant. As per some studies, when the size of hematoma is >30 cm^3, the morbidity and mortality increases significantly[8].

V. Discussion

As per age distribution, in our study, 100% mortality was noted in age group 70-79 yrs., 80-89 yrs. and >90 yrs. In our study for sex distribution, out of 65 patients, 55.3 % were males and 44.6% were females. Thus the ratio of male to female was 1.2:1. There was no significant association was found in male and female sex and poor outcome. (p value-0.497). For history of hypertension, in our study 61.5% were known case of hypertension, out of them 55% patients expired. Rest 38.4% patients were freshly detected cases of hypertension. Our hospital gets patients from lower socioeconomic strata with poor education. Our history for Diabetes Mellitus shows out of 65 patients, 21.5% patients had H/O diabetes, out of which 85.7 % expired. The GC score established significant correlation between the Glasgow coma scale on admission and poor outcome. (p=0.002). In our study for site of hematoma, high mortality was not significantly associated with No. of sites of hemorrhage (p=0.07). However, the increasing No. of hemorrhages is associated with increasing mortality. Most patients had multiple sites of hemorrhage at the time of presentation. Therefore, prognosis on the basis of site (basal ganglia, thalamus, lobar, brain stem, cerebellar) was not possible. The volume of hemorrhage study shows the volume of intracerebral hemorrhage >10,000 mm3 is considered a severe stroke and proven as poor prognostic parameter for 30 days' mortality outcome. (p value =0.0001).

VI. Conclusion

Glasgow coma scale on admission is significant for poor prognosis. Number of sites of hemorrhage in a CT scan is not significant with poor outcome. The volume of the hemorrhage is significant for poor outcome of stroke.

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Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Impact of Gender on Dementia in Elderly Urban Population

By Dr. Mrs. Gayatri Godbole, Shrirang Godbole & Dr. Mrs. Savita Vaidya

Bharati Vidyapeeth Medical College

Abstract- Dementia is characterized by progressive deterioration in intellectual, cognitive and judgmental functions of the brain. It is associated with high levels of dependency and morbidity. Therefore early detection and prevention is more important.

Material and Methods: 300 subjects aged 60 years and above were screened with MMSE. MMSE scores above 23 indicate normal cognitive function and score of < 23 indicates both the likelihood of cognitive impairment.

Results: Amongst the study population, 66 subjects had a MMSE score less than 23. Out of the total male subjects 11.47% had cognitive impairment. Out of the total female subjects 29.21% of females had cognitive impairment.

Conclusion: In a given sample, cognitive impairment is more prevalent in females than males.

Keywords: *elderly population, cognitive impairment, MMSE, gender.*

GJMR- A Classification: *NLMC Code: WM 220*

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Impact of Gender on Dementia in Elderly Urban Population

Dr. Mrs. Gayatri Godbole [α], Shrirang Godbole [σ] & Dr. Mrs. Savita Vaidya [ρ]

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Conclusion: in a given sample, cognitive impairment is more prevalent in females than males.

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I. Introduction

The percentage of elderly populace across the globe is increasing day by day and dementia is emerging as an important health problem in them.[1] Dementia is characterized by progressive deterioration in intellectual, cognitive and judgmental functions of the brain. Dementia is an irreversible clinical syndrome. It is associated with high levels of dependency and morbidity.

As the patient is increasingly dependent on other people, it becomes a great burden for him as well as his family[2]. Additionally, associated co-morbid conditions may complicate their status. Dementia even reduces the lifespan of the affected person.

The disease is insidious in onset and progress gradually. The patient slowly moves from bad to worse. People don't take the symptoms seriously and think of it as a natural, normal process associated with advanced age. This we owe to the fact that there is less awareness about this condition in the population at large. It remains a reality that most of these cases are undetected for long or remain undiagnosed. The patients present to the clinician at a very late stage, where treatment may not have the expected benefits. As the incidence of dementia grows, the pinch of this reality is being acutely felt.

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Dementia is increasing in tandem with the increasing life expectancies worldwide. This increase is resulting in huge socio-economical consequences on patients, caregivers and even communities everywhere. After taking into consideration various etiologies of dementia, age and gender remain important non-modifiable risk factors. Some researchers state that women are at higher risk of developing Alzheimer's disease. They show a higher prevalence and increased rate of cognitive decline.[3] While a survey conducted by Sunil Kumar Raina in residents aged 60 years and above concludes that there is no significant difference in cognitive scores between males and females.[4]

Of the other causes of dementia, some can be treated partially but others cannot. Hence, early detection, in order to prevent further deterioration, has gained much significance.[5] This will help in instituting symptomatic treatment early and thus help to delay the progression of the disease.

The Mini Mental State Examination (MMSE) is a tool used for early identification and assessment of dementia.[6] It assesses cognitive function in depth, through a series of questions which have their respective scores. People are then categorized based on their scores. It is comparatively an easy tool to use and analyze. Also it is well understood by the patients. This makes it a near perfect screening tool. Comprehensive neuropsychiatric and medical examinations are necessary to diagnose dementia. They are too expensive and time consuming to be used in such studies done in primary settings. Hence, a screening tool like the MMSE is valuable for early detection of dementia.

Therefore this study was planned to screen people for dementia using MMSE and to correlate it with their gender.

Aim: To screen for dementia in the elderly and to the study the impact of gender
on it.

II. Objectives

1. To screen elderly people for dementia using Mini Mental State Examination (MMSE) Questionnaire.
2. To evaluate effect of gender on dementia.

III. Methodology

It was a cross sectional community based study in urban area. People above 60 years of age were

included in the study. Known cases of dementia or depression and subjects with severe hearing impairment were excluded.

300 Residents (males and females) aged 60 years and above were identified randomly. Detailed interview of the subject and informant was taken and clinical examination of the subject was conducted. Demographic variable were noted down.

Subjects were administered Mini Mental State Examination (MMSE) which is known as the gold standard for cognitive screening.[7] It assesses cognitive function in relation to orientation, memory, attention and calculation, language and visual construction. It has 11 questions and the maximum score is 30. MMSE scores above 23 indicate normal cognitive function and score of < 23 indicates both the likelihood of cognitive impairment and the need for further evaluation.

Subjects with MMSE score <23 in both sexes were compared.

IV. Results

A total of 300 subjects were interviewed .The study population consisted of 122 males and 178 females. Amongst them, 66 subjects had a MMSE score less than 23(Table no.1). Out of the total male subjects 11.47% had cognitive impairment. Out of the total female subjects 29.21% of females had cognitive impairment(Table no.2).

V. Discussion

Dementia is a major contributor towards disability amongst the elderly population. In this study total 300 people were assessed using the MMSE. Amongst the study population, 66 subjects had a MMSE score less than 23(Table no.1). This group comprised of 52 females & 14 males. Out of 122 males in study population, 11.47% had cognitive impairment. In females, out of 178 total females 29.21% were cognitively impaired subjects(Table no.2). We can thus conclude that, it is more prevalent in females. Therefore gender is a non-modifiable risk factor for dementia.

The American Alzheimer Association also postulates that at an age above 60 years the risk of an average female getting dementia is 1in 6 compared to an average male, who has a risk of 1 in 116.8 Other researches carried out in this field had similar results.

Luine et al. and Goodman et al. quote that estrogen plays a major role in this phenomenon. Estrogen has been reported to have beneficial effects on the brain, possibly acting as a protective factor in AD via its ability to promote the growth, survival and activity of cholinergic neurons.9, 10 The hypothesis that sex hormones affect the response of the patient to acetylcholinesterase inhibitors is the basis of this important (which are an important treatment modality) has also garnered substantial evidence.

Scerri et al. quote that an emerging risk factor in dementia is depression.11 The greater the frequency and severity of depressive symptoms, the greater are the risks. On an average, women have higher rates of depression than men and that is related to more prevalence of cognitive impairment in females.

The variable survival rates between men and women might affect the outcome here. Hence it is prudent to extend due caution before coming to any conclusion. On the contrary Prencipe and coworkers had concluded that prevalence rates did not differ in both sexes in Alzheimer and vascular dementia.12

A multitude of factors interact to give rise to the difference in dementia prevalence among men and women. Influence of genetic factors which predispose some to dementia is important. The neuroprotective effect of estrogen cannot be understated. Lastly, cultural and psychosocial factors have a lasting impact as far as gender prevalence is concerned. It is interesting to note that Indian women are more actively engaged in artistic and group activities; they are adept at socializing.

On the other hand an overall lower level of education & poor nutritional status of women put them on back foot. The interplay of these factors is an important aspect of the etiology here. But in the case of women, their advantages are often undermined by their shortcomings. This goes hand in hand with the findings of this study. After taking cognizance of the results, we can reasonably conclude that in a given sample, cognitive impairment is more prevalent in females than males.

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Table no. 1: Sex distribution in study group

Parameter (Sex)	Frequency	Percentage (%)
Males	122	40.66 %
Females	178	59.34%
Total	300	100%

Table no. 1 shows that out of total 300 subjects 40.66 % were males and 59.34% were females.

Table no. 2: MMSE score in male and female subjects

Sex	MMSE score	Frequency	Percentage
Males	> 23	108	88.52
	< 23	14	11.47
	Total	122	100
Females	> 23	126	70.78
	< 23	52	29.21
	Total	178	100

Table no. 2 shows that in the total study population, subjects with scores below 23 were 22%. It constituted 11.47% of the total male subjects and females constituted 29.21% of total females in the study group.

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Global Journal of Medical Research: a
Neurology and Nervous System
Volume 16 Issue 2 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Early Diagnosis of Neuron Mitochondrial Dysfunction May Reverse Global Metabolic and Neurodegenerative Disease

By Martins IJ

University of Western Australia

Editorial- The rise in obesity and diabetes in various countries have reached epidemic proportions [1] with the inability of the brain to regulate body weight and energy balance in the early part of life and related to neurodegenerative disease in these countries. Neurons in the brain become sensitive to Western diets with alterations in neurons that lead to brain circuitry disorders or feeding signals [2]. In insulin resistance and neurodegenerative diseases the astrocyte-neuron interaction is defective in the brain [3] and consumption of a Western diet does not allow neurons to metabolize glucose and fatty acids but instead leads to mitochondrial apoptosis and programmed neuron death. In the periphery in global communities liver steatosis can be reversible with hepatocyte mitochondria still able to metabolize fatty acids and glucose after consumption of a healthy low calorie diet but in the brain neuron mitochondria may not continue with mitochondrial biogenesis but continue to undergo apoptosis with neuron death.

GJMR- A Classification: *NLMC Code: WL 358.5*

EARLYDIAGNOSISOFNEURONMITOCHONDRIALDYSFUNCTIONMAYREVERSEGLOBALMETABOLICANDNEURODEGENERATIVEDISEASE

Strictly as per the compliance and regulations of:

Editorial

Early Diagnosis of Neuron Mitochondrial Dysfunction May Reverse Global Metabolic and Neurodegenerative Disease

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Editorial

The rise in obesity and diabetes in various countries have reached epidemic proportions [1] with the inability of the brain to regulate body weight and energy balance in the early part of life and related to neurodegenerative disease in these countries. Neurons in the brain become sensitive to Western diets with alterations in neurons that lead to brain circuitry disorders or feeding signals [2]. In insulin resistance and neurodegenerative diseases the astrocyte-neuron interaction is defective in the brain [3] and consumption of a Western diet does not allow neurons to metabolize glucose and fatty acids but instead leads to mitochondrial apoptosis and programmed neuron death. In the periphery in global communities liver steatosis can be reversible with hepatocyte mitochondria still able to metabolize fatty acids and glucose after consumption of a healthy low calorie diet but in the brain neuron mitochondria may not continue with mitochondrial biogenesis but continue to undergo apoptosis with neuron death.

Networks between various brain cells involve membrane and nuclear lipid signals with diets involved in the regulation, transmission and communication between various brain cells. The three main types of glial cells are the astrocytes, oligodendrocytes and microglia with astrocytes involved with the maintenance of endothelial cells in brain capillaries and the blood brain barrier (BBB) to prevent toxic substances and their entry into the brain with the prevention of mitochondrial apoptosis in neurons. Astrocytes have been shown to be important to neuron lifespan and survival [4,5] with diets and lifestyle involved with epigenetic modification that disrupt astrocyte signalling [3] involved in the maintenance of neurons in individuals in global populations. Nutritional diets that prevent epigenetic alterations include DNA methylation, covalent histone modification and non-coding RNAs that are involved in gene activation and repression with chromatin structure modifications associated withintact circadian regulation critical for the increased survival of astrocytes and neurons. Atherogenic diets that stimulate bacterial lipopolysaccharides (LPS), mycotoxin and xenobiotics into the central nervous system may induce various cellular stresses with the induction of mitochondrial apoptosis induced neurodegenerative diseases.

The increased global susceptibility to insulin resistance associated with brain aging and neurodegenerative diseases now indicate neuron vulnerability to senescence or apoptosis [6]and require early plasma biomarker diagnosis that may assist with reversal of neuron senescence to healthy neurons that may be interpreted from lipidomic tests, genomic tests and proteomic tests [7]. The information provided from these tests now are relevant to the early diagnosis of neuron senescence and linked to mitochondrial biogenesis versus mitochondrial apoptosis that determine the lifespan of neurons. The tests may further assist in novel and important Alzheimer's disease therapeutics that reverse amyloid beta oligomers damage to neuronsin diabetes related neurodegenerative disease and Alzheimer's disease [8].

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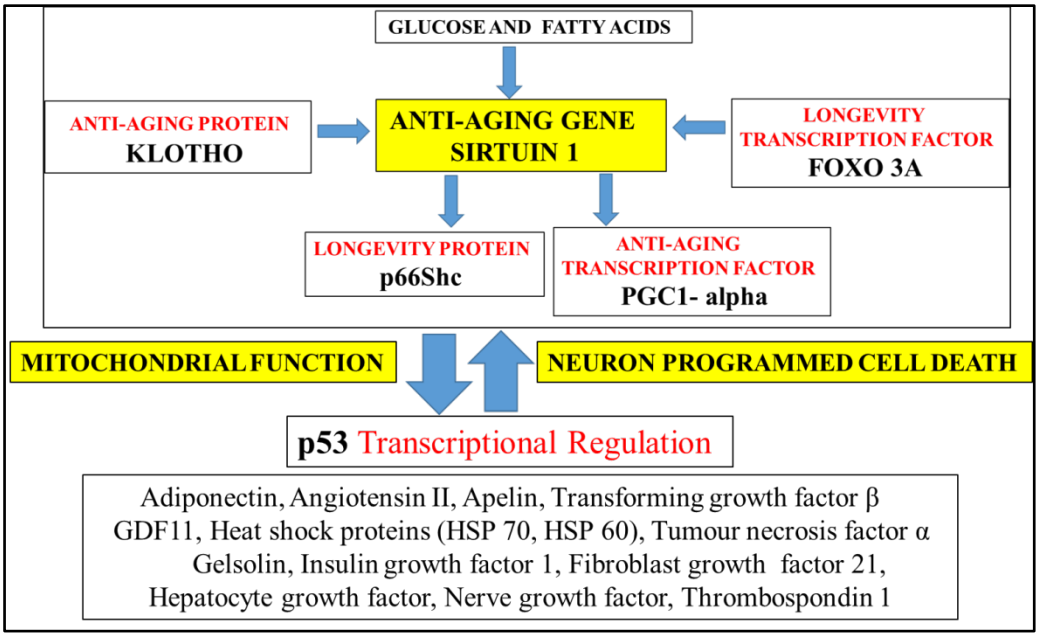

Figure 1: Downregulation of the calorie sensitive gene Sirtuin 1 is important to mitochondrial biogenesis with Sirt 1/pr53 regulation of other anti-aging genes such as Klotho, p66shc, Foxo3a and the anti-aging transcription factor PGC1-alpha involved in mitochondrial function. Plasma protein analysis for the diagnosis of neuron mitochondrial function has become important with neurodegeneration closely linked to the global diabetic epidemic, NAFLD and various chronic diseases. Proteins such as apelin, angiotensin II, gelsolin, heat shock proteins, thrombospondin 1, transforming growth factor beta, tumour necrosis factor alpha, insulin like growth factor 1, fibroblast growth factor 21, adiponectin, GDF11 and hepatocyte growth factorare involved with mitochondrial survival and may involve p53 regulation of mitochondrial function in metabolic and neurodegenerative diseases.

Genomic analysis now indicate that the anti-aging gene Sirtuin 1 (Sirt 1) regulates other anti-aging genes that are now critical to mitochondrial biogenesis and neuron proliferation [8]. Sirt 1's regulation of mitochondria involve p53 regulation and include other anti-aging genes (Figure 1) that synthesize the Klotho anti-aging protein, p66shc longevity protein and transcription factors such as Forkhead box O3(FOXO3a) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 apha) that are essential for the maintenance of mitochondrial function in cells [9-11]. In Figure 1 the plasma proteome analysis of various proteins may now indicate the diagnosis of neuron apoptosis versus neuron survival from the determination of plasma proteins that are relevant to mitochondrial biogenesis versus mitochondrial apoptosis. The plasma proteome analysis for neuron survival that involve mitochondrial health include proteins such as apelin, angiotensin II, gelsolin, heat shock proteins (HSP 70, HSP 60), thrombospondin 1 (TSP-1), Transforming growth factor beta (TGF beta), Tumour necrosis factor alpha (TNF alpha), Insulin like growth factor 1 (IGF-1), Fibroblast growth factor 21 (FGF21), adiponectin, GDF11 and hepatocyte growth factor (HGF). Dysregulated crosstalk between the adipose tissue and the liver [10] alter the release of these proteins with low and defective transport of these proteins to neurons in the brain relevant to increased mitochondrial senescence versus mitochondrial biogenesis.

The gene-environment interaction identifies Sirt 1 in many global populations as the defective gene involved in the defective nuclear-mitochondria interactions in the adipose tissue and the liver relevant to the mitochondrial theory of aging [12-14].Sirt 1 (nicotinamide adenine dinucleotide dependent class III histone deacetylase) targets transcription factors such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC 1-<alpha>), p53, pregnane X receptor (PXR), peroxisome proliferator-activated receptor (PPAR) to adapt gene expression to mitochondrial function with relevance to metabolic activity, insulin resistance and inflammation. Sirt 1 is involved in chromatin remodelling with effects on the nuclear and mitochondria interactions that determine neuron proliferation via mitochondrial biogenesis by deacetylation of PGC 1 alpha and p53 transcription factors that are important to mitochondrial DNA homeostasis [15-19]. Sirt 1's regulation of circadian clocks regulate mitochondrial function that determine neuron synaptic plasticity in various neurological diseases [10, 20-34]. Major commercial interests in simple proteome tests that can be conducted in any routine laboratory may now indicate from plasma proteome analysis the proliferation of mitochondria with relevance to neuron survival and prevention of

programmed cell death. In the current global non alcoholic fatty liver disease (NAFLD) epidemic the various proteins are important to neuron mitochondrial biogenesis and alterations in these proteins in the blood plasma may be involved in mitochondrial apoptosis and determine early neuron cell death. Sirt 1 and Sirt 3 are both involved with neuron mitochondria function with Sirt 1's important role in circadian regulation of Sirt 3's regulation of mitochondrial function [35,36].However with the aging process various plasma proteins are now relevant to mitochondrial health by the regulation of Sirt 1/p53 expression (**Figure 1**) that may involve astrocyte regulation of mitochondrial biogenesis versus apoptosis that determine synaptic dysfunction and neurodegeneration [37-39].

HGF has also been shown to be important to neuron and axon survival with relevance to HGF in p53 transcriptional regulation and mitochondrial biogenesis [40-49]. FGF 21 is regulated by Sirt 1 and is a biomarker for mitochondrial disease with relevance to neuronal mitochondrial apoptosis [50-53]. Apelin and Angiotensin II [54-56] regulate mitochondrial function via Sirt 1 [57] with both peptides involved with mitochondrial function and apoptosis. HSP 60 and 70 regulate mitochondrial function with Sirt 1 involved in the metabolism of HSP 60 and 70 [58-60]. Gelsolin and its involvement in mitochondrial survival involves p53 transcriptional regulation to maintain mitochondrial health in metabolic disease and aging [61-63]. NGF regulates the circadian clock with effects on p53 regulation of neuron mitochondrial function [64-75]. IGF-1 and GDF11 are now important to maintain mitochondrial function [76,77] with its connections to Sirt 1/IGF-1/GH regulation by diet and nutrition [78]. TNF alpha [79] is particularly sensitive to mitochondrial induced neuronal apoptosis and with TGF beta [80] overide Sirt 1'scontrol of circadian regulation with relevance to mitochondrial related neuron apoptosis [81,82].

Adiponectin levels are closely connected to mitochondrial biogenesis with Sirt 1 regulation important toadiponection gene expression [83-87]. Plasma TSP1 levels have become important to mitochondrial apoptosis with levels of LPS involved in TSP1 regulation and Sirt 1 repression [7]. TSP1effects on CD47 receptor to prevent mitochondrial biogenesis and TSP-1 effects on p53 expression override Sirt 1/p53 transcriptional regulation of neuron synapticity and survival [88-93]. Sirt 1 regulation of brain derived neurotrophic factor (BDNF) is now important to BDNF induced mitochondrial function and synaptic plasticity [9]. Early analysis of plasma proteins (**Figure 1**) that determine mitochondrial survival by p53 transcriptional regulation may now be important to Sirt 1 metabolism of toxic oligomers such as amyloid beta and alpha synuclein in neurodegenerative diseases [9,10].

Furthermore plasma lipidomic analysis allow interpretation that in insulin resistance and neurodegenerative diseases the increased plasma ceramides and sphingosine 1 phosphate are associated with increased liver/neuron mitochondrial apoptosis with programmed cell death of neurons associated with Sirt 1 repression. Lipids such as ceramides have been shown to inhibit Sirt 1/p53 transcriptional regulation and induce cell death in neurons or hepatocytes [94,95]. In contrast sphingosine 1 phosphate may act as a Sirt 1 activator by actions on increased PGC1alpha levels with increased mitochondrial biogenesis [96]. Ceramides supersede the effects of various plasma proteins (**Figure 1**) that have been shown to regulate p53 transcriptional activityto prevent mitochondrial apoptosis with relevance to neuron differentiation with plasma ceramide levels important to mitochondrial related defects in synaptic plasticity and neurodegeneration [3,7].

Nutritional therapy is required to promote the nuclear-mitochondria interaction andprevent mitochondrial apoptosis with improvement in the astrocyte-neuron crosstalk that determines the lifespan of neurons[97]. Diet and nutrition is particularly relevant to neuron Sirt 1 regulation of the circadian rhythm with relevance to mitochondrial biogenesis and the prevention of high glucose induced mitochondrial dysfunction in neurons [98]. The effects of high fat diets that contain palmitic acid induce liver steatosis and steastosis may be reversible but accelerated mitochondrial disease in neurons [99-103] by palmitic acid as a Sirt 1 inhibitor may induce irreversible neurodegenerative disease [53]. Nutriproteomic diets [7] have become important by the release from the adipose tissue and liver of proteins essential for the maintenance of the nuclear-mitochondria crosstalk in neurons. In the developing world nutritional therapy may be superseded with relevance to xenobiotic induced mitochondrial apoptosis [104] with accelerated synaptic plasticity defects and neurodegeneration. Activators of Sirt 1 such as leucine may be essential for mitochondrial biogenesis [105,106] and with stress disorders the apelinergic system defects [57] may lead to accelerated mitochondrial apoptosis with neuroendocrine disease. Interests in nutritional therapy include Sirt 1 activators such as pyrroloquinoline quinone, resveratroland rutin [107-110] that specifically stimulate mitochondria biogenesisin the liver and brain compared with ochratoxin A [111] that interferes with mitochondrial respiration.

Conclusion

Interests in the early diagnosis of neuron senescence has become a major concern for many global communities with accelerated neurodegeneration involved with the metabolic syndrome and various chronic diseases. The mitochondria in neurons are sensitive to dysregulation with irreversible defects in these mitochondria that result in neuron apoptosis early

in life. The plasma proteins such as Apelin, Angiotensin II, Gelsolin, Heat shock proteins (HSP 70, HSP 60), Thrombospondin 1 (TSP-1), Transforming growth factor beta (TGF beta), Tumour necrosis factor alpha (TNF alpha), Insulin like growth factor 1 (IGF-1), Fibroblast growth factor 21 (FGF21), GDF11, Adiponectin and Hepatocyte growth factor (HGF) should be measured early in life to determine mitochondrial damage in brain cells. The importance of the plasma profile is now relevant to assessment by nutritional therapy to reverse and halt neuron loss that is irreversible with relevance to the accelerated neurodegeneration and early nutritional regulation has become critical to the reversal of the global NAFLD, metabolic syndrome and chronic diseases.

Acknowledgements

This work was supported by grants from Edith Cowan University, the McCusker Alzheimer's Research Foundation and the National Health and Medical Research Council.

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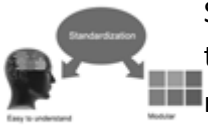

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Before start writing a good quality Computer Science Research Paper, let us first understand what is Computer Science Research Paper? So, Computer Science Research Paper is the paper which is written by professionals or scientists who are associated to Computer Science and Information Technology, or doing research study in these areas. If you are novel to this field then you can consult about this field from your supervisor or guide.

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.

8. Use the Internet for help: An excellent start for your paper can be by using the Google. It is an excellent search engine, where you can have your doubts resolved. You may also read some answers for the frequent question how to write my research paper or find model research paper. From the internet library you can download books. If you have all required books make important reading selecting and analyzing the specified information. Then put together research paper sketch out.

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.

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

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 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.

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 lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to 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

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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."
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- 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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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
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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ISSN 9755896