Sudan University of Science and Technology

College of Graduated Studies

Characterization of Brain Lesions by Magnetic Resonance Spectroscopy MRS

توصيف افات الدماغ باستخدام التصوير بالرنين المغناطيسي الطيفي

A Thesis Submitted for Fulfillment of the Requirement of PhD in Diagnostic Radiological Imaging

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2021

الآيـة

بِسْمِ اللَّهِ الـرَّحْمَنِ الـرَّحِيمِ

قـال تـعـالـى:

﴿ اقْـرَأْ بِـاسْمِ رَبِّـكَ الَّـذِي خَـلَـقَ * خَـلَـقَ الْإِنْـسَـانَ مِـنْ عَـلَـقٍ * اقْـرَأْ وَرَبُّـكَ الْأَكْـرَمُ * الَّـذِي عَـلَّـمَ بِـالْـقَـلَـمِ * عَـلَّـمَ الْإِنْـسَـانَ مَـا لَـمْ يَـعْـلَـمْ ﴾

سورة الـعـلـق[5 - 1]:

Dedication

This work is lovingly dedicated:

To my Mather, sisters and daughters for their help and support

To my sister the soul mates “sawsan gasim” for her valuable support.

To my Friend “DR .Awadia Gareeballah” for her help, understanding and encouragement

To my friends for their valuable advice and helps

To the all dearest people in my life

Acknowledgment

I am grateful to God who gave me determination, strength, and potency to evaluate and assess the information of my study and investigation. I am extremely thankful to my supervisor [Prof. ASMA IBRAHIM] who developed my abilities with her advices and motivation. The knowledge and skills of my supervisor have always been a source of motivation for me. Her advices resulted in the deletions and additions in the original work.

I would like to express my sincerely thank the participants without whom the study would not have been feasible. The Sudan University of Science and Technology, College of Medical Radiological Science and Royal car international hospital, Almoalem medical city hospital, Khartoum Sudan are thankfully for Radiology department and staffs, I would like to express special thanks to my daughter Ebtisam Al-harth. My Mother, My Sisters, and my friends.

I would like to thank everyone who assisted by one way or another to bring this study to the light.

Abstract

The study was retrospective conducted at Almoalem medical city hospital ,Royal car international hospital, , Khartoum- Sudan during the period from the 2017—2020. The study aims to characterized the different of brain lesions using single-voxel Proton Magnetic Resonance Spectroscopy (MRS). The main problem of the study that the diagnosis of brain lesions was more complicated and histopathology for it was very difficult so that MRS can lead to proper diagnosis and decrease using of histopathology.

The study population were 200 patients and was collected from the record system (PACS) of MRI department of Almoalem Medical Center (A) 100 patient's male and female at any age, male 54. female 46 using semines MRI machine 1.5 Tesla and 100 patient in Royal care international hospital (B), male 54 female46 using Toshiba Excelart Vantage 1.5 Tesla MRI machine, all patient In both hospitals do MRI brain for the patients by lies supine on the examination couch with their head within the head coil, the head is adjusted so that the inter papillary line is parallel to the couch , then applied the MR protocols (T1, T2, diffusion and flair). T1weighted image after intravenous gadolinium administration were obtained at least 2 planes After MRI image done, then MRS is done, using selective metabolites Cho , Cr, NAA ,Lipid/Lac , Cho/Cr and NAA/Cr ratio in Different Brain Lesion. The metabolite ratios were assessed and compared to different lesions using independent sample t-test and ANOVA tests ,in group A total of 100 patients (54 males and 46 females; mean age was 43.75 years) were examined. The most prevalent brain lesions were glioblastoma multiform (GBM) and glioma (24% and 22%). The Cho/Cr ratio was higher in GBM and lymphoma than other brain lesions (4.37 and 4.25 respectively). The NAA/Cr ratio is lower in lymphoma, tuberculoma, inflammation, and abscess (0.6, 1.2, 1.4, and 1.85). The Cho/Cr ratio was significantly higher in neoplastic brain lesions than non neoplastic one (3.95 vs. 1.74, p-value < 0.001). The non neoplastic brain lesions had significantly lower peaks of Cho/Cr than neoplastic lesions which have higher peak. GBM and lymphoma have the highest Cho/Cr ratio compared to other brain lesions but not-significant difference in NAA/Cr ratio ($p > 0.05$) , for neoplastic Cho/Cr ratio is very high while NAA/Cr is low compare to none neoplastic lesion. NAA is reduced in 93%and absent in 7% of cases , 45% of the lesion causes moderate elevation of lipid lactate, 31% mild elevation while in 21 % the lipid lactate is normal and in 3% there is normal lipid lactate and alanine peak seen in cases of meningioma.

Total of 100 patients (54 male and 46 females at any age) were examined. After the data collection from PACS of Royal care hospital (group B), metabolites describe is Cho ,Cr, NAA ,Lipid/Lac , Cho/Cr ratio data was then analyzed using statistical package for social sciences version 23, frequency and percentage used for categorical variable, cross tabulation using Chi square test to correlate between study variables,. The study found that the most frequent location of brain lesion in MRI is cerebrum 59%. The most common brain lesion described by MRS are low grade glioma is 18%, high grade glioma is 12%, gliomatosis cerebri 5%, focal encephalitis 3%, TB granuloma 4%. The Cho/Cr is done and show that the minimum ratio 1.10 in non-neoplastic Lesion, maximum ratio 8 in high grade tumor. Most (86%) of these brain lesions yield low NAA. The lipid/lactate may be moderate or mildly elevated In 33% of cases, respectively. Significant correlation found between lesion types suggesting on MRS and metabolites values ($p < 0.01$) as lipid lactate producing sky high peak on different types of non-neoplastic eg. Granuloma, normal peak in all cases of meningioma.

The study concluded that MRS complementary to MRI in characterization of brain lesions, it can assess the lesion type and helping in grading of brain tumors.

The study recommended that doing MRS routinely in patients with brain lesions to Improve the accuracy of neuro diagnosis and for other benefit in patient management such as, differentiation between tumor and tumor like lesions, encouraging more studies to be done in MRS with a Larger sample size and comparison with other imaging and histopathology Findings, which is the small lesion need Magnetic resonance spectroscopic imaging (MRSI) rather than Single- voxel spectroscopy (SVS) Because of the large voxel size limitations and the length of time of image acquisition, MRS is needed to characterizing the lesion types and put the program of treatment before surgery, so that needs to increase diagnostic centers of MRS in Sudan.

مستخلص الدراسة

في الوقت الحاضر يعتبر التشخيص بالرنين المغنطيسي الطيفي واحد من طرق التصوير الأساسية لتقييم آفات الدماغ المختلفة. لا يزال تشخيص أورام الدماغ الأولية والثانوية وغيرها من آفات الكتلة البؤرية داخل الجمجمة بناءًعلي نتائج التصوير بالرنين المغنطيسي وحده يمثل مشكلة صعبة, يعتبر التحليل بالرنين المغناطيسي الطيفي (MRS) أداة تشخيصية فعالة وآمنة للتصوير ومفيدة لتقييم آفات الدماغ المختلفة. يعطي الرنين المغناطيسي الطيفي البروتوني (H-MRS1) معلومات مختلفة تمامًا تتعلق بتكاثر غشاء الخلية ، وتلف الخلايا العصبية ، واستقلاب الطاقة ، والتحول النخري في أنسجة المخ أو الورم. تمت إضافة الفائدة السريرية لـ H-MRS1 إلى التصوير بالرنين المغناطيسي للتميز بين الآفات الورمية وغير الورمية داخل الجمجمة (Moll er 2001).

أجريت هذه الدراسة بأثر رجعي من وحدة الارشفه لمستشفى مدينة المعلم الطبية و مستشفى رويال كير الدولي ، الخرطوم - السودان خلال الفترة من 2017 - 2020.

تهدف الدراسة إلى تمييز آفات الدماغ المختلفة باستخدام التحليل الطيفي للرنين المغناطيسي البروتوني أحادي الفوكسل. كانت المشكلة الرئيسية للدراسة هي أن تشخيص آفات الدماغ أكثر تعقيدًا وأن التشريح للمرضي صعبًا للغاية بحيث يمكن التشخيص المناسب وتقليل استخدام علم الأنسجة عن طريق آلة التصوير بالرنين المغناطيسي الطيفي.

كانت الدراسة لمئاتين 200 مريض تم جمعهم من نظام االارشفه PACS لقسم التصوير بالرنين المغناطيسي في مركز المعلم الطبي (أ) مائه مريض من الذكور54 والإناث 46 في اعمار مختلفة ، باستخدام آلة التصوير بالرنين المغناطيسي 1.5 تسلا سيمنس و 100 مريض في مستشفى رويال كير (ب) ،الذكر 54 الأناث 46 باستخدام جهاز الرنين المغنطيسي 1.5 تسلا توشيبا. جميع المرضى في كلا المستشفيين قامو بإجراء التصوير بالرنين المغناطيسي من خلال الاستلقاء على طاولة الفحص مع وضع رأسهم داخل ملف الرأس ، يتم ضبط الرأس بحيث يكون الخط الحليمي الداخلي موازيًا للطاولة ، ثم تطبق البروتوكولات التالية (T1, T2flair). تم عمل 1T بعد إعطاء الجادولينيوم في الوريد في وضعين من فحص التصوير بالرنين المغناطيسي وتم إجراء الفحص بالرنين المغنطيسي الطيفي MRS ، باستخدام الكولين ، الكرياتين، الان استايل اسبرتيت ، نسبة الدهون واللاكتيت ونسبة الان استايل اسبرتيت والكرياتين. في آفات الدماغ المختلفة تم تقييم نسب المستقلب ومقارنتها مع الآفات المختلفة باستخدام عينة مستقلة من اختبار t واختبارات ANOVA ، في المجموعة (أ) كانت الآفات الدماغية الأكثر انتشارًا هي الورم الدبقي متعدد الأشكال القليوبلاستوما ملتي فورم (GBM) والورم الدبقي قليوما (24٪ و 22٪). كانت نسبة الكولين كرياتين أعلى في القليوبلاستوما ملتي فورم GBM والورم الليمفاوي من آفات الدماغ الأخرى (4.37 و 4.25 على التوالي). نسبة الكولين كرياتين أقل في الأورام اللمفاوية وورم السل ، والالتهاب ، والخراج (0.6 - 1.2 - 1.4 - 1.85). كانت نسبة الكولين كرياتين أعلى بشكل ملحوظ في الأورام كانت نسبة الكولين كرياتين أعلى بشكل ملحوظ في آفات الدماغ الورمية مقارنة بآفات الأورام غير الورمية (3.95 مقابل 1.74) ، قيمة $p>0.001$. كان لآفات الدماغ غير الورمية قمم أقل بشكل ملحوظ في نسبة الكولين كرياتين من الآفات الورمية التي لها ذروة أعلى. تمتلك القليو بلاس توما ملتي فورم والورم الليمفاوي أعلى نسبة الكولين للكرياتين مقارنة بآفات الدماغ الأخرى ولكن ليس هناك فرق كبير في النسبة , $p> 0.05$ ، بالنسبة للأورام الكولين للكرياتين نسبة عالية جدًا بينما نسبة الان استايل اسبرتيت للكرياتين منخفضة مقارنة بآفات غير ورمية وان الان استايل اسبرتيت قليل في 93٪ وغير موجود في 7٪ من الحالات ، و 45٪ من الآفة تسبب ارتفاعًا كبيرا في اللاكتيت الدهنية و 31٪

ارتفاعًا معتدلًا ، بينما في 21٪ يكون اللاكتيت الدهنية أمرًا طبيعيًا وفي 3٪ يوجد لاكتيت دهنية طبيعية ووجود ذروة ألانين في حالات الورم السحائي. تم فحص إجمالي 100 مريض {54 ذكور و 46 إناث في اعمار مختلفه}. بعد جمع البيانات من وحدة الارشفه ال PACS لمستشفى رويال كير(المجموعة ب) ، المستقلبات في الدراسه هي الكولين ، الكرياتين، الان استايل اسبرتيت ، نسبة الدهون واللاكتيت ، تم تحليل بيانات نسبة الكولين والكرياتين باستخدام الحزمة الإحصائية للعلوم الاجتماعية الإصدار 23 ، التكرار والنسبة المئوية المستخدمة لـ متغير فئوي ، جداول متقاطعة باستخدام اختبار Chi square للربط بين متغيرات الدراسة. وجدت الدراسة أن الموقع الأكثر شيوعًا لآفة الدماغ في التصوير بالرنين المغناطيسي هو المخ 59٪. أكثر الآفات الدماغية شيوعًا التي وصفتها هي الورم الدبقي منخفض الدرجة بنسبة 18٪ ، الورم الدبقي عالي الدرجة بنسبة 12٪ ، الورم الدبقي المخي 5٪ ، التهاب الدماغ البؤري 3٪ ، ورم السل الحبيبي 4٪. تم إجراء التحليل ووضح أن الحد الأدنى للنسبة 1.10 في الآفة غير الورمية ، والنسبة القصوى 8 في الورم عالي الدرجة. ونتج (٪86) من آفات الدماغ لها نسبة منخفضة من الان استايل اسبرتيت ، وقد كانت نسبة الدهون واللاكتيت معتدلاً أو مرتفعًا بشكل معتدل في 33% من الحالات ، على التوالي. تم العثور على ارتباط كبير بين أنواع الآفات التي يشار اليها بالرنين المغنطيسي الطيفي وقيم المستقلبات ($p<0.01$) مثل اللاكتيت الدهنية التي تنتج ذروة السماء و أنواع مختلفة من غير الورمية على سبيل المثال الورم الحبيبي ،بينما في جميع حالات الورم السحائي الذروة تكون طبيعية.

وخلصت الدراسة إلى ان الرنين المغنطيسي الطيفي مكمل للتصوير بالرنين المغناطيسي في توصيف آفات الدماغ ، ويمكنه تقييم نوع الآفة والمساعدة في تصنيف أورام المخ.

يوصي الباحث بإجراء الفحص بالرنين المغنطيسي الطيفي بشكل روتيني في المرضى الذين يعانون من آفات الدماغ لتحسين دقة التشخيص العصبي وللاستفادة الأخرى في إدارة المرضى مثل التمايز بين الأورام والأورام مثل الآفات ، وتشجيع المزيد من الدراسات التي يجب إجراؤها في الرنين المغنطيسي الطيفي مع حجم عينات أكبر و مقارنتها مع نتائج التصوير الأخرى ونتائج التشريح للمرضي ، وأن الآفات الصغيرة تحتاج إلى التصوير الطيفي بالرنين المغناطيسي متعدد الفوكسل بدلاً من التحليل الطيفي أحادي الفوكسل نظرًا لقيود حجم الفوكسل الكبير وطول وقت الحصول على الصورة ،كما يوصي إجراء الرنين المغنطيسي الطيفي لأجل توصيف أنواع الأورام قبل الجراحة ليتم وضع برنامج العلاج قبل الجراحة وزيادة مراكز التشخيص بالرنين المغنطيسي الطيفي في السودان.

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List of abbreviations

Abbreviation	Full meaning
1H-MRS	Proton Magnetic Resonance Spectroscopy
2D	2-dimensional
3D	3-dimensional
AA	Amino Acid
Ala	Alanine
Ac	Acetate
ANOVA	Analysis of variance
CHESS	Chemical-Shift Selective expiation
Cho	Choline
Cr	Creatine
P Cr	Phospho Creatine
CNS	Central nervous system
CSI	Chemical shift imaging
Fig	Figure
FID	Free Induction Decay
FOV	Field of view
FLAIR	Fluid Attenuated Inversion Recovery
GBM	Glioblastoma multiforme
Gd	Gadolinium
Glu	Glutamate
GLN	Glutamine
Glx	Composed peak of Glu and Gln
HGG	High-grade glioma
lac	Lactate
Lip	Lipid
LGG	Low-grade glioma
Max	Maximum
MI	Myo-inositol
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance spectroscopic imaging
NAA	N-acetyl aspartate
NMR	Nuclear magnetic resonance
PC L	Primary central nervous system lymphoma

PRESS	Point -resolved spectroscopy
RF	Radio frequency
ROI	Region of interest
SE	Spin echo
SNR	Signal-to-noise-ratio
STEAM	Stimulated echo acquisition mode
SVS	Single-voxel spectroscopy
T1	Longitudinal relaxation time in units of ms
T2	Transverse relaxation time in units of ms
TE	Echo time in unit of ms
TI	Inversion time
TR	Repetition time in unit of ms
VOI	Volume of interest
WHO	World Health Organization

Chapter One
Introduction

Chapter One
Introduction

1.1 Introduction

Brain is an important part of human body, brain lesions are a type of damage, injury, or abnormal change to any a part of the brain ,can caused by many different factors like family history , trauma, infection due to harmful germs or bacteria in the brain, tumors that either start in the brain(primary tumors) or travel there (metastatic) via blood or lymphatic vessels and exposure to radiation or certain chemicals which is increase the chance of tumors and lesions in the brain . A brain tumor are abnormal mass of tissue in which cells cross, multiply and uncontrollably classified on bases of tissue of origin, the tumor is classify as primary or secondary and metastatic. (Cube and Discovery, 2012). Brain tumors are the second leading cause of cancer death in children under 15 years and young Adults up to the age of 34. These tumors are also the second fastest growing cause of cancer death among humans older than 65 years .Early detection and correct treatment based on accurate diagnosis are important steps to improve disease out come. Under physiological conditions, several important metabolites are observed Brain tumor is of two main types which are benign tumor or malignant tumor (neoplasm) for most neoplasm, the term malignant is used to describe the lack of cell differentiation ,the invasive nature of the tumors and its ability to metastasizes, in the brain, however, even a well differentiated and histological benign tumor may grow and cause death because of its location, it's difficult to classify as purely benign or malignant without finally diagnosis by Biopsy , most of the time the biopsy is done during surgery called (an open biopsy) or performed as aspirate procedure called a needle biopsy (Lukas et al., 2004; Cube and Discovery, 2012).But by using a modern imaging methods diagnosis and characterization of brain lesions before surgery, these imaging modalities like magnetic resonance spectroscopy (MRS) which allows non invasive and in vivo exploration of the molecular composition

of tissue; it is procedure used to asses chemical abnormalities in body tissue such as the brain (Yan, 2002). MRS may be used to assess disorder like infection of the brain, stroke, multiple sclerosis and tumors. MRS is similar to MRI, expect that it measures the function of the brain rather than it's structures, it also shows some features of brain tumors that my not clear on an MRI scan and it's identifies certain molecular constituents - the metabolites - involved in physiological or pathological processes, even though sectors copy can be performed on different nuclei, we focus here on the spectroscopy of the hydrogen nucleus, by for the most widely studied in clinical MRI,MR image depend on magnetic resonance signal of hydrogen nuclei, hydrogen nuclei are present in very high concentrations in water, then other hydrogen –containing metabolites are present but with low concentrations these metabolites can contribute to the MR signal if the water signal is suppressed. Currently magnetic resonance spectroscopy (MRS) in combination with magnetic resonance imaging(MRI) are important tools to identify the location, size and type of brain lesion. So far, MRS has been proven to be an accurate non-invasive technique which can give detailed chemical information of metabolites present in the suspected brain lesion (KOWALCZYK, 2013).

1.2 Importance of the study:

In Sudan: Brain lesions is one of the major causes of death and tripping of life especially in children, and diagnosis and characterized of lesions is need an investigation is costly but the majority of patients are poor. So that Magnetic Resonances Spectroscopy (MRS) is more sensitive and accurate in diagnosis and characterized of brain lesions.

1.3 Problem of the study:

The knowledge and diagnosis the lesion types is a accurately done by Biopsy which is difficult and invasive and high cost, so non invasive Methods are needed to study the chemical components abnormalities as well as characterizing the lesions types. MRS can study the concentrations of different

chemical components within tissues and characterized the lesions before surgery to put the program of treatment before surgery unfortunately these modalities is found in restricted center in Sudan.

1.4 Objectives of the study

1.4.1 General objective:

The General Objectives of the study characterized of Brain lesions by Magnetic Resonances Spectroscopy (MRS).

1.4.2 Specific objectives:

- To asses distribution of gender ,age ,NAA and lipid ,Descriptive statistic for age , Cho/Cr and NAA/Cr ratios.
- Cho/Cr and NAA/Cr ratios in different brain lesions.
- To compare Cho/Cr and NAA/Cr ratios in neoplastic and non neoplastic brain lesions by (independent sample t-test).
- To demonstrate MRI finding.
- To demonstrate MRS finding.
- To correlate MRS finding and NAA.
- To correlate MRS finding and Lipid/ Lactate
- To compare means Cho/Cr and NAA/Cr ratios with MRS finding

Chapter Two
Theoretical Background and previous Studies

Chapter Two

Theoretical Background and previous Studies

The central nervous system (CNS) is composed of the brain and spinal cord.

The peripheral nervous system (PNS) is composed of spinal nerves that branch from the spinal cord and cranial nerves that branch from the brain ,The PNS includes the autonomic nervous system, which controls vital functions such as breathing, digestion, heart rate, and secretion of hormones(Singh, 2015)

The brain is made up of two types of cells: nerve cells (neurons) and glia cells. Neurons have two "processes" called axons and dendrites. The glial cells have only one neurons can generate action potentials, glial cells cannot however, glial cells do have a resting potential. Neurons have synapses that use neurotransmitters. The glial cells do not have chemical synapses(S. Snell, 2010).It is also proposed that the basic functional unit in the brain is defined by how neurons communicate, and consists of two neurons and their interconnecting dendritic-synaptic-dendritic field. Since a functional unit is composed of two neurons, it requires two structural units to form a functional unit. (*Snell, Richard S, 2010)* In addition to these two types, there are the cells of the meninges which cover the central nervous system, the blood vessels which enter it and the nerves which arise from it. The nerve cells:-are very variable in size and shape, but all of them have cytoplasmic process these processes are two types, Axons and dendrites. The dendrites are processes which receive Stimuli from the axons of the nerve cells that end on them. The axons are usually thinner than the dendrites, it transmit impulses from the cell body either to other nerve cells, or to peripheral tissues through myelin sheath, the axons together with its myelin sheath is known as a nerve fiber. The axon form bundles (tracts), while the cell bodies with their associated dendrites form clusters (nuclei) Because of their difference in colour in the fresh state, the tracts form the white mater of the (CNS), while the nuclei make up the grey mater the glial cells: The cells of the brain that provide neurons with

nourishment, protection, and structural support. it is about 10 to 50 times more than nerve cells and are the most common type of cells involved in brain tumors, It also consist of four types of cells are star-shaped cells— they regulate the blood brain barrier, allowing nutrients and molecules to interact with neurons; They control homeostasis, neuronal defense and repair, scar formation, and also affect electrical impulses. Oligodendroglia: are small cells with few, short processes they are found surrounding nerve cell bodies and on their dendrites they create a fatty substance called myelin that insulates axons – allowing electrical messages to travel faster.Microglia: are the brain's immune cells, protecting it from invaders and cleaning up debris. these small cells are often rod-shaped they are difficult to identify in the normal nervous system, only becoming readily visible where there is tissue damage (Singh, 2015).

Ependymal cells line the ventricles and secrete cerebrospinal fluid (CSF).

The brain is organ that controls all functions of the body, interprets information from the outside world, and embodies the essence of the mind and soul. Intelligence, creativity, emotion, and memory are a few of the many things governed by the brain protected within the skull, the brain receives information through our five senses: sight, smell, touch, taste, and hearing - often many at one time. It assembles the messages in a way that has meaning for us, and can store that information in our memory (Gilks, 2017).

2.1 The brain:

The brain controls our thoughts, memory and speech, movement of the arms and legs, and the function of many organs within our body, the brain is composed of the cerebrum, cerebellum, and brainstem . figure (2.1).

(Okumura A, et al, 2012)

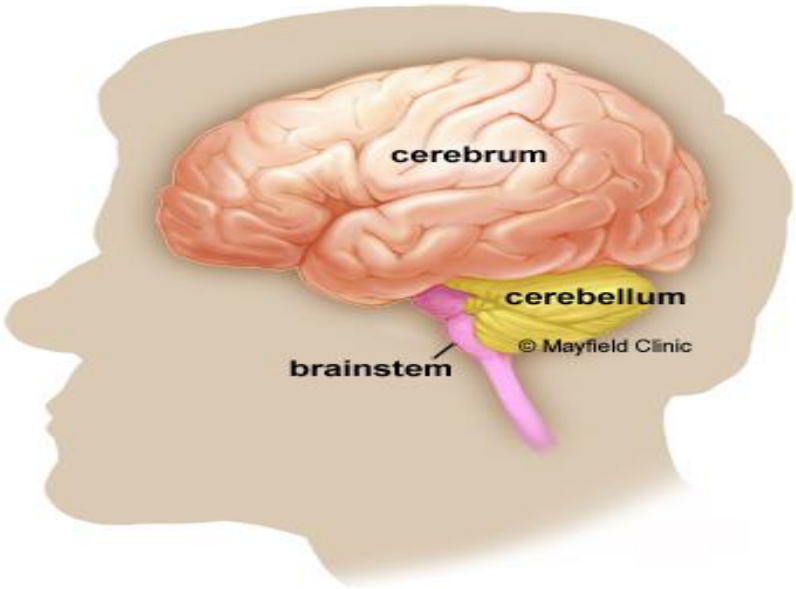

Figure2. 1 The three main parts: the cerebrum, cerebellum and brainstem(Tamraz and Comair, 2006)

2.1.1Cerebrum:

The cerebrum is the largest part of the brain is composed of the right and left cerebral hemisphere which are connected by a mass of white matter called corpus callosum that transmits messages from one side to the other show figure (2.2) . Each hemisphere controls the opposite side of the body. If a brain tumor is located on the right side of the brain, your left arm or leg may be weak or paralyzed. Not all functions of the hemispheres are shared. In general, the left hemisphere controls speech, comprehension, arithmetic, and writing. The right hemisphere controls creativity, spatial ability, artistic, and musical skills. The left hemisphere is dominant in hand use and language in about 92% of people If a stroke occurs on the right side of the brain your left arm or leg may be weak or paralyzed, the hemispheres are separated by the longitudinal fissure, into which projects the flax cerebri. (Fehrenbach ,et al,2015) .

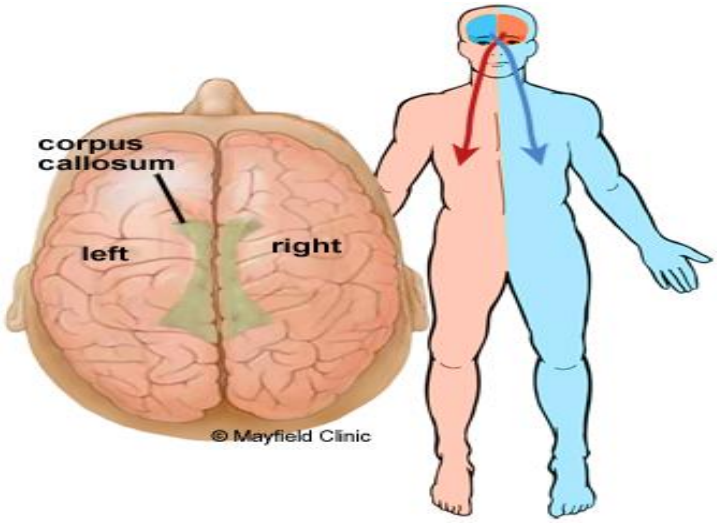

Figure 2.2 left and right hemispheres of the cerebrum(Mayfield Brain & Spine 2016)

The cerebrum is divided into left and right hemispheres. The two sides are connected by the nerve fibers corpus callosum. not all functions of the hemispheres are shared. In general, the left hemisphere controls speech, comprehension, arithmetic, and writing. The right hemisphere controls creativity, spatial ability, artistic, and musical skills. (*Snell, Richard S, 2010*) The left hemisphere is dominant in hand use and language in about 92% of people. Each cerebral hemisphere IS divided into four lobes the frontal, parietal, temporal and the occipital lobe. Each cerebral hemisphere is composed of an outer layer of grey matter called the cerebral cortex, the surface of the cerebral cortex is arranged in a number of folds, called gyri, which are separated by sulci or fissures, the most important sulci are: The central sulcus, which runs downwards from the upper medial surface of the cerebral cortex, and separates the frontal and parietal lobes and lateral sulcus, which lies on the inferior and lateral aspects of the cerebral hemisphere, and separates the temporal lobe from the frontal and parietal lobe. .(*Snell, Richard S, 2010*).

2.1.1.1The most important gyri are:

The precentral gyrus, which lies in front of the central sulcus, post central

gyrus, which lies behind the central sulcus.(*Snell, Richard S, 2010*).

2.1.1.2The motor area: the pre central gyrus is frequently called the motor cortex, and from this area all voluntary movement are initiated, the nervous impulses from the motor cortex pass to muscles of the opposite side of the body, thus the right cerebral cortex controls the muscles of the left side of the body and vice versa.(*Snell, Richard S, 2010*).

2.1.1.3The sensory area: the post central gyrus is frequently called the sensory cortex, it receives and appreciates all general sensation from the opposite side of the body, and thus the right cerebral cortex appreciates sensations from the left side of the body and vice versa.(*Snell, Richard S, 2010*).

2.1.1.4The auditory area: the cortex of the temporal lobe immediately below the lateral sulcus is called the auditory area, and is concerned with the appreciation of impulses from the inner ear which are transmitted in the auditory nerve. (*Snell, Richard S, 2010*).

2.1.1.5 The visual area: the cortex of the greater part of the occipital lobe is called the visual area, and it receives impulses from the retina which are transmitted in the optic nerves. (*Snell, Richard S . 2010*)

2.1.1.6 The motor speech area: the cortex of the frontal lobe, just above the anterior end of the lateral sulcus is called speech area and is concerned with initiating the voluntary movement which produce speech, this area is found in the left cerebral cortex in right-handed persons and vice versa. The cavity present within each cerebral hemisphere is called the lateral ventricle, the lateral ventricles communicate with the third ventricle through the inter ventricular foramina. (Fehrenbach, et al, 2015).

2.1.1.7 Lobes of the brain

The cerebral hemispheres have distinct fissures, which divide the brain into lobes. Each hemisphere has 4 lobes: frontal, temporal, parietal, and occipital (Fig2.3). Each lobe may be divided, once again, into areas that serve very specific functions. It’s important to understand that each lobe of the brain does

not function alone. There are very complex relationships between the lobes of the brain and between the right and left hemispheres.***(****Snell, Richard S. 2010****)***

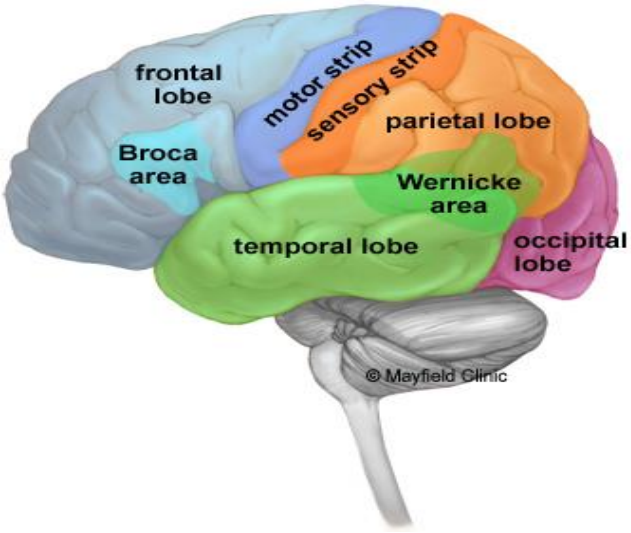

Figure 2.3 The cerebrum is divided into four lobes: frontal, parietal, occipital and temporal(Tamraz and Comair, 2006).

2.1.2 The Diencephalon:

The diencephalon is almost completely hidden from the surface of the brain, it consists of a dorsal thalamus, a ventral hypothalamus and epithalamus.

figure (2.4) .(*Snell, Richard S, 2010*).

2.1.2.1 The thalamus is a large mass of grey matter that lies on either side of the third ventricle and acts primarily as relay center through which all sensory information (except smell) passes on the way to the cerebrum it's also involved in consciousness ,sleep and memory. .(*Snell, Richard S, 2010*).

2.1.2.2 The epithalamus is serves as a connection between the limbic system and other parts of the brain the limbic system a parts of the brain that is involved with emotion, long –term memory and behavior.(*Snell, Richard S, 2010*).

2.1.2.3 The hypothalamus forms the lower part of the lateral wall and floor of the third ventricle. The following structures are found _ in the floor of the third ventricles from before backward: The optic chiasma, the tubercinereum, the

infundibulum, and the mammillary bodies, this hypothalamus is extremely important brain region. It contains neural centers for hunger thirst and the regulation of the body temperature and regulation of the pituitary gland secretion. In addition, centers in the hypothalamus contribute to the regulation of sleep, wakefulness, sexual arousal, performance and emotions such as anger, fear, pain and pressure, neurons within the supra -optic and paraventricular nuclei of the hypothalamus produce anti diuretic hormone (which stimulates the kidneys to reabsorb water and thus to excrete a smaller volume of urine) and it produce oxytocin hormone. .(*Snell, Richard S, 2010*).

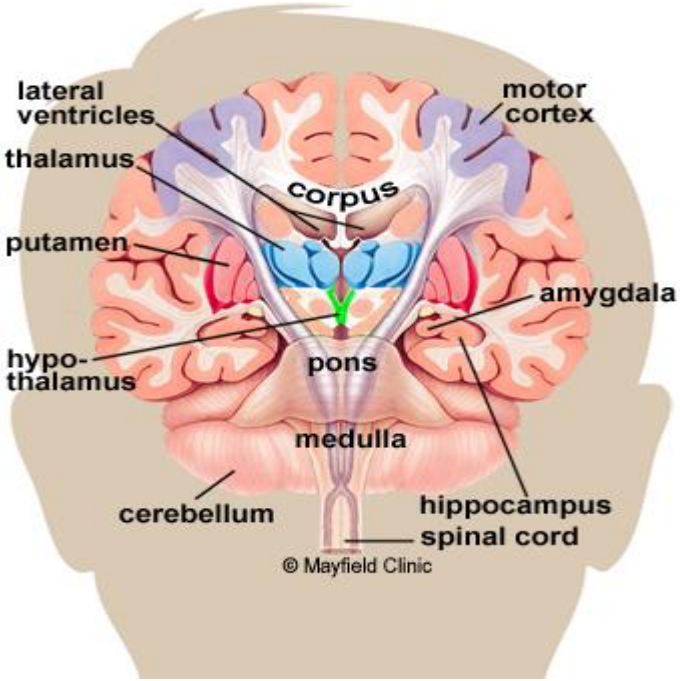

Figure 2.4 Coronal cross-section showing the Diencephalon

(Mayfield Brain& Spine 2016)

2.1.3 The Brainstem: It is stalk like in shape and connects the narrow spinal cord with the expanded forebrain. is made up of the medulla oblongata, the Pons and the midbrain and occupies the posterior cranial fossa of the skull. It performs many automatic functions such as breathing, heart rate, body temperature, wake and sleep cycles, digestion, sneezing, coughing, vomiting, and swallowing (*Snell, Richard S, 2010*).

2.1.3.1 The Mid Brain:

The mid brain is the narrow part of the brain that passes through the tentorial notch and connects the forebrain to the hind brain(*Snell, Richard S, 2010*)

The mid brain composed of two lateral halves, called the cerebral peduncles, each of these is divided into an anterior part, the crus cerebri, and a posterior part, the tegmuntum, by a pigmented and band of grey matter, the substantia nigra. The narrow cavity of the midbrain is the cerebral aqueduct, which connects the third and fourth ventricles, the tectum is the part of the mid brain posterior to the cerebral aqueduct. It has four small surface swellings, the upper two of these, called the superior colliculi, are involved in visual reflexes, the posterior two called the inferior colliculli, are relay centers for auditory information, the colliculi, are deeply placed between the cerebellum and the cerebral hemispheres. The pineal body is a small glandular structure that lies between the superior colliculi, it is attached by a stalk to the region of the posterior wall of the third ventricles, a small recess of the ventricles, called the pineal recess, extends into the base of the stalk, the pineal commonly calcifies in middle age and functions it are not fully understood, but there is evidence that it produces pharmacologically-active substances, e.g. melatonin and serotonin, and influences gonadal growth in those animals in which this occurs in response to increasing exposure to light. (*Snell, Richard S, 2010*)

2.1.3.2 The Pons: is situated on the anterior surface of the cerebellum below the mid brain and above the medulla oblongata, it is composed mainly of nerve fibers, which connect the two halves of the cerebellum, it also contains ascending and descending fibers connecting the forebrain, the mid brain, and the spinal cord within the pons are several nuclei associated with specific cranial nerves, the trigeminal, abducens, facial and vestibulocochlear nerves. Other nuclei of the pons co-operate with nuclei in the medulla oblongata to regulate breathing. The two respiratory control centers in the pons are known as the apneustic and the pneumotaxic centers(*Snell,, 2010*)

2.1.3.3 The medulla oblongata:

Is along stem-like structure and connects the Pons above to the spinal cord below, all of the descending and ascending fiber tracts that provide communication between the spinal cord and the brain pass through the medulla, these fiber tracts cross to the contra lateral side in elevated, triangular structures in Medulla called pyramids, so that the left side of the brain receives sensory information from the right side of the body and vice versa. Similarly, because of the decussating fibers, the right side of the brain controls motor activity in the left side of the body and vice versa. There are several important nuclei within the medulla, the nucleus ambiguus and hypoglossal nucleus give rise to several cranial nerves like auditory and glossopharyngeal nerve(*Snell, 2010*)

2.1.4 The Cerebellum:

It located under the cerebrum coordinating the muscle movements, Lies within the posterior cranial fossa beneath the tentorium cerebelli, it is situated posterior to the pons and the medulla oblongata, it consist of two hemispheres connected by a median portion, the vermis. The cerebellum is composed of an outer cortex of grey matter and has white matter in its internal part, the outer surface of the cerebellum is thrown into a large number of narrow folds which are separated by deep fissures. The cerebellum is connected to the mid brain, by the superior cerebellar peduncles, to the pons by the middle cerebellar peduncle, and to the medulla by the inferior cerebellar peduncles. (*Snell, Richard S, 2010*)

2.1.5 The Meninges:

The meninges are three layers of protective tissue called the dura mater, arachnoid mater, and pia mater that surround the neuraxis. The meninges of the brain and spinal cord are continuous, being linked through the magnum foramen. (Okumura A, et al, 2012)

2.1.5.1 The dura mater:

Is the outer most layers of the meninges and it is a thick dense membrane, it divides into two layers, the outer layer acts as the periosteum of the inner surface of the bones which form the cranial vault, the inner layer acts as a protective covering for the brain. The two layers are, in the main closely united, but the inner layers separated from the outer layer at several sites. The venous sinuses, which drain the venous blood from the brain, lie between the two layers of the dura mater.(*Snell, Richard S, 2010*)

The falx cerbri, which projects into the longitudinal fissure between the left and right cerebral hemispheres, is a sickle shaped fold of the inner layer of the dura matter. The superior sagittal sinus runs in the upper margin of the falx cerebri and the inferior sagittal sinus in the lower free margin.The tentorium cerebelli, which partially covers the posterior cranial fossa, is a cresentic-shaped fold of the inner layer of the dura mater, it lies between the upper surface of the cerebellum and the occipital lobes of the cerebral hemispheres. The posterior and lateral margins of the tentorium cerebelli enclose the transverse sinuses. The posterior margin of the falx cerebri is attached to the tentorium in the mid line and the straight sinus runs back-wards in the line of attachment. (*Snell, Richard S, 2010*)

2.1.5.2 The functions of falx and tentorium:

These tough folds of dura mater play an important part in stabilizing the brain within the cranial cavity and prevent this semi fluid structure oscillating freely when the head is moved suddenly. When the brain does move within the cranial cavity, it carries the pia and arachnoid with it, and throws considerable stress on the very thin-walled veins which traverse the subdural space to the venous sinuses, which are held fasten by the dura mater. (*Snell, Richard S, 2010*)

2.1.5.3 The arachnoid mater:

Is the middle layer of the meninges, it develop from a single mass of loose connective tissue, it is a thin delicate membrane which is separated from the

dura matter by a narrow space called the subdural space, this space contains a thin film of fluid. The arachnoid matter projects in small tufts into the superior sagittal and transverse sinuses to form structures called the arachnoid granulations.(*Snell, Richard S, 2010*)

2.1.5.4 The piamater:

Is the innermost layer of the meninges and is separated from the arachnoid matter by a fluid-filled space called the subarachnoid space. The pia matter is a thin membrane which is composed of fine areolar tissue containing large number of small blood vessels. The pia matter forms the telachoroidea of the roof of the third ventricle and fourth ventricle of the brain, and it fuses with the ependyma to form the choroid plexuses in the lateral, third and fourth ventricles of the brain. From this special vascular tufts (choroids plexuses) the cerebrospinal fluid (CSF) is mainly derived to the cavities of the brain (ventricles) from which it escapes into the subarachnoid space The (CSF) in addition to its metabolic functions, it forms a sort of protective water bath around the brain and spinal cord. (*Snell, , 2010*)

2.1.6 The Ventricles of the Brain: (fig 2.5)

The ventricles of the brain are inter-communicating, fluid filled spaces which lie within the cerebrum, the mid brain, the Pons and the medulla oblongata.

2.1.6.1 The lateral ventricle:

The two lateral ventricles lie one on each side of the midline in the substance of the cerebral hemispheres, they each have an anterior horn which extends into the frontal lobe, a posterior horn which extends into the occipital lobe and temporal horn which extends into temporal lobe. The posterior part of the anterior horn opens into a narrow canal called the inter ventricular foramen, which unites the two lateral ventricles and extends downwards to open into the upper part of the third ventricle at an opening called the foramen of monro. (*Snell, Richard S, 2010*)

2.1.6.2 The third ventricle:

This is a narrow, slit-like cavity which lies in the midline between the two thalami, the foramen of Monro opens into its upper anterior angle, the lower anterior angle projects downwards towards the pituitary gland and is called the infundibular recess Just anterior to it's a small recess, called the optic recess, which lies over the optic chiasma, the posterior border of the third ventricles is related to the pineal gland.(*Snell, Richard S, 2010*)

2.1.6.3 The aqueduct of sylvius:

The cerebral aqueduct is a narrow canal, which runs through the mid brain from the lower posterior angle of the third ventricle to open into the fourth ventricle.
(*Snell, Richard S, 2010*).

2.1.6.4 The fourth ventricle:

Lies in front of the cerebellum and behind the pons and the upper part of the medulla oblongata, on each side of the fourth ventricle a recess, called the lateral recess, there are foramina in the roof of the fourth ventricle' through which the ventricular system communicates with the subarachnoid space, the foramina of Magendie lies in the midline of the roof, and the foramina of Luschka lie in the roofs of the lateral recesses.*(Tamraz,et al2006).*

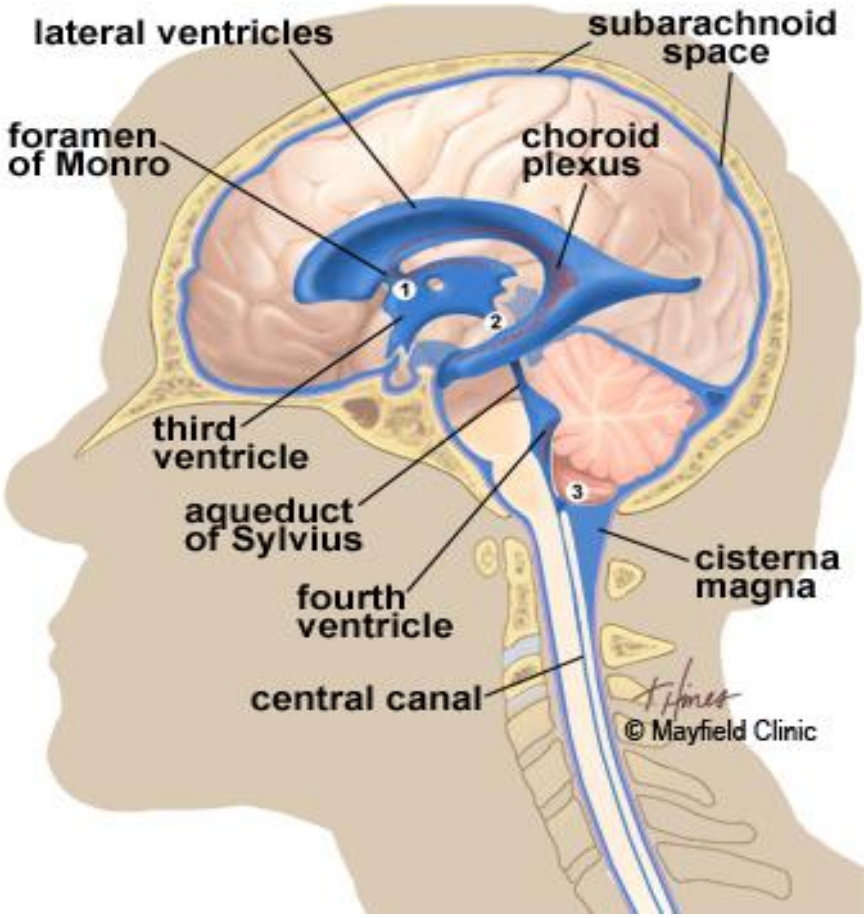

Figure 2.5 CSF is produced inside the ventricles deep within the brain. CSF fluid circulates inside the brain and spinal cord and then outside to the subarachnoid space(Tamraz and Comair, 2006).

2.1.7 Pituitary gland:

The pituitary gland lies in the pituitary fossa immediately inferior to the hypothalamus and measure 12 mm in its transverse diameter and 8 mm in its antero-posterior diameter. The pituitary gland has a stalk, the infundibulum, which arises from the tubercinereum in the floor of the third ventricle, The anterior lobe is five times larger than the posterior lobe. Neurons in the hypothalamus produce hormones known as releasing hormones and inhibiting hormones, which are transported by the blood (hypophyseal portal vein) to the anterior lobe of the pituitary these hormones regulate the secretion of this lobe by this means, regulate the secretion of other endocrine glands. The posterior

lobe is made up of nerve fibers whose cell bodies lie in the hypothalamus and release hormones in response to impulses from these nerves. The anterior lobe is adherent to the posterior lobe by a narrow zone called the pars inter media (Jaspan and Griffiths, 2004).

2.1.8 Blood supply

The brain by is supplied by two the internal carotid arteries and the two vertebral arteries. The four arteries lie within the subarachnoid space ,and their branches anastomose on the inferior surface of the brain to form the circle of Willis. (Fig. 6), the internal carotid arteries supply most of the cerebrum. The vertebral arteries supply the cerebellum, brainstem, and the underside of the cerebrum after passing through the skull the right and left vertebral arteries join together to form the basilar artery, The basilar artery and the internal carotid arteries “communicate” with each other at the base of the brain called the Circle of Willis (Fig.6). The communication between the internal carotid and vertebral-basilar systems is an important safety feature of the brain. If one of the major vessels becomes blocked, it is possible for collateral blood flow to come across the Circle of Willis and prevent brain damage. (*Snell, Richard S, 2010*).

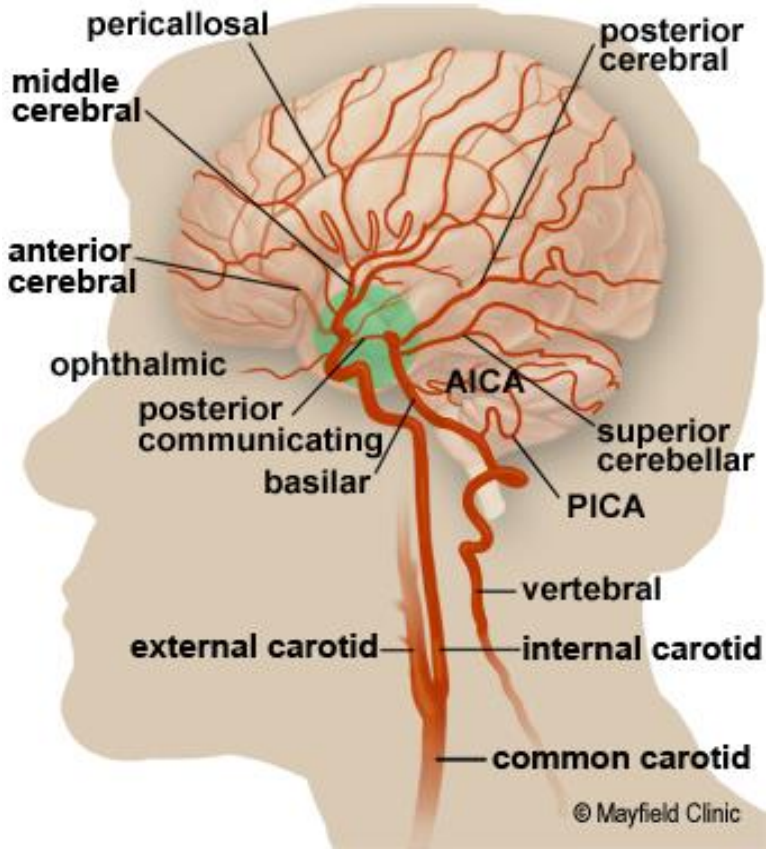

Figure 2. 6 The common carotid artery courses up the neck and divides into the internal and external carotid arteries. The brain's anterior circulation is fed by the internal carotid arteries (ICA) and the posterior circulation is fed by the vertebral arteries (VA).The two systems connect at the Circle of Willis (Mayfield Brain& Spine 2016)

2.1.9 Veins of the brain:

The veins of the brain have no vascular tissue in their thin walls, and they possess no valves they emerge from the brain and drain into cranial venous sinuses. Cerebral and cerebella veins and viena of brain stem are present, the great cerebral veins is formed by union of the two internal cerebral veins and drains into the straight sinus. (Okumura A, et al, 2012)

2.1.10 the cranial nerves:

The cranial nerves are twelve (12) pairs of nerves, two of these pairs arise from neuron cell bodies located in the forebrain and ten pairs arise from the mid brain

and brain stem. The cranial nerves are referred to either by numbers or by names they are: (figure .7). Olfactory nerve (contains sensory fibers):Its concerned with the sense of smell, the fibers of the nerve arise in the mucous membranes of the olfactory area of the nose and enter the olfactory bulb which lies on the under surface of the frontal lobe of the cerebral hemisphere and passes backwards to the cortex of the temporal lobe of the cerebral hemisphere.(Singh, 2015). Optic nerve (contains sensory fibers): Its concerned with the sense of sight, the fibers originate in the retina of the eye, enter the cranial cavity through the optic foramen, and from the nasal half of the retina cross in the optic chiasma. The nerve runs backwards to the visual area in the cerebral cortex of the occipital lobe.The oculomotor nerve (contains motor fibers): The fibers of the nerve arise from the grey matter in the mid brain and then leave the brain to run forward to enter the orbit, this nerve supplies all the muscles which move the eye, except the lateral rectus and superior oblique muscles. (*Snell, Richard S. 2010).*

The trochlear nerve (contain motor fibers): the fibers of the nerve arise from grey matter in the mid brain, it supplies the superior oblique muscle of the eye.

The trigeminal nerve (contains sensory and motor fibers): It arise by two roots a sensory root and motor root, from the pons, the fibers of the sensory root pass through ganglion called trigeminal ganglion, which lies on the floor of the cranial cavity.The motor 'fibers arise from the grey matter in the upper part of the pons. The sensory fibers divide into three main branches which are called the ophthalmic division, the maxillary division and the mandibular division. (Singh, 2015). The abducens nerve (contains motor fibers): The fibers of the nerve arise from grey matter in the pons and leave the brain at the lower border of the pons, the nerve supplies the lateral rectus muscle of the eye. The facial nerve (contains motor and sensory fibers) The motor fibers arise from grey matter in the lower part of the pons, the sensory fibers pass to the taste area in the lower part of the precentral gyrus of the cerebral cortex.(Singh, 2015).

The auditory nerve (contains sensory fibers): These sensory fibers are of two types: The cochlear fibers and the vestibular fibers. The two groups of fibers unite and enter the cranial cavity through the internal auditory canal and enter the cranial cavity through the internal auditory meatus to pass to the lower border of the pons. The nerve then enters the brain just below the facial nerve, the cochlear fibers pass to the auditory area in the temporal lobe of the cerebral hemisphere the vestibular fibers pass to the cerebellum.The gloss pharyngeal nerve (contains sensory and motor fibers): The motor fibers from grey matter in the medulla oblongata, the sensory fibers carry general sensation to the brain from the pharynx and tongue. The vagus nerve (contain motor and sensory fibers): it arises mainly from grey matter in the medulla oblongata and leaves the brain as more small roots from the side of the medulla oblongata to pass downwards. This nerve supplies many branches of the body. The accessory nerve (contains motor fibers): Is formed from two roots. One of which arises from the medulla oblongata and the other from the spinal cord, the two roots supply some of muscles like the soft palate, the trapezium.The hypoglossal nerve (contains motor fibers): These fibers arise from grey matter in the lower part of the medulla oblongata and leave the brain as a series of small roots which arise from the side of the medulla oblongata interiorly to the roots of the vagus nerve, this nerve supplies the muscle of the tongue and hyoid bone. (Okumura A, et al, 2012).

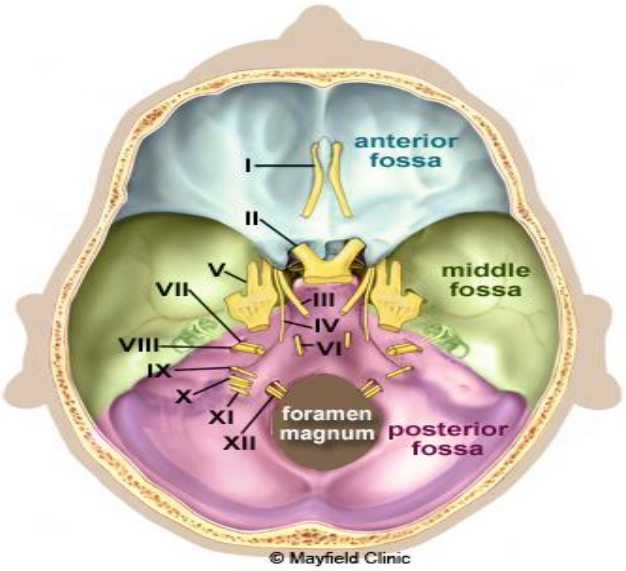

Figure 2.7 Represent twelve (12) pairs of cranial nerves

(Tamraz and Comair, 2006)

TABLE 2.1 The Roman numeral, name, and main function of the twelve cranial nerves:(Tamraz , et al 2006).

Number	Name	Function
I	Olfactory	smell
II	Optic	sight
III	Oculomotor	moves eye, pupil
IV	Trochlear	moves eye
V	Trigeminal	face sensation
VI	Abducens	moves eye
VII	Facial	Movesface, salivate
VIII	Vestibulocochlear	hearing, balance
IX	Glossopharyngeal	taste, swallow
X	Vagus	Heart rate, digestion
XI	Accessory	moves head
XII	Hypoglossal	moves tongue

2-2 Physiology of The Brain:

2.2.1 The Cerebrum

The cerebrum consists of two hemispheres (right and left) connected by a white matter bridge called the corpus callosum. Each hemisphere controls the opposite side of the body .Is divided into lobes, the frontal, parietal, temporal and occipital lobe , each lobe may be divided, once again, into areas that serve very specific functions. It's important to understand that each lobe of the brain does not function alone. There are very complex relationships between the lobes of the brain and between the right and left hemispheres. (Poretti A, et al2016).

2.2.1.1Frontal lobe

Personality, behavior, emotions ,Judgment, planning, problem solving, Speech speaking and writing (Broca's area)Body movement (motor strip)Intelligence, concentration, self awareness. (Fehrenbach et al 2015).

2.2.1.2Parietal lobe

Interprets language, words, Sense of touch, pain, temperature (sensory strip)
Interprets signals from vision, hearing, motor, sensory and memory Spatial and visual perception. (Fehrenbach et al 2015).

2.2.1.3Occipital lobe

Interprets vision (color, light, movement)

2.2.1.4Temporal lobe

Understanding language (Wernicke's area)Memory, Hearing ,Sequencing and organization . (Fehrenbach et al 2015).

2.2.2 The Brainstem

The brain stem acts as a relay center connecting the cerebrum and cerebellum to the spinal cord. It performs many automatic functions such as breathing, heart rate, body temperature, wake and sleep cycles, digestion, sneezing, coughing, vomiting, and swallowing .

2.2.2.1 The pons

Within the pons are several nuclei associated with specific cranial nerves, the trigeminal, abducens, facial and vestibulocochlear nerves. Other nuclei of the pons co-operate with nuclei in the medulla oblongata to regulate breathing. The two respiratory control centers in the pons are known as the apneustic and the pneumotaxic centers(*Snell, Richard S, 2010*)

2.2.3The cerebellum

The cerebellum receives sensory inputs from the muscles and joints of the body and uses this information to keep the body balanced and to maintain posture. The cerebellum also controls the timing and finesse of complex motor actions such as walking, writing, and speech. (Okumura A, et al, 2012).

2.2.4 The Basal ganglia

It includes the caudate, putamen and globus pallidus These nuclei work with the cerebellum to coordinate fine motions, such as fingertip movements. They are strongly interconnected with the cerebral cortex, thalamus, and brainstem, as well as several other brain areas. The basal ganglia are associated with a variety of functions, including control of voluntary motor movements, procedural learning, habit learning, eye movements, cognition, and emotion. ***(Snell, Richard S. 2010).***

2.2.5TheVentricles and cerebrospinal fluid

The brain has hollow fluid filled cavities called ventricles .Inside the ventricles is a ribbon like structure called the choroid plexus that makes clear colorless cerebrospinal fluid (CSF). CSF flows within and around the brain and spinal cord to help cushion it from injury. This circulating fluid is constantly being absorbed and replenished. There are two ventricles deep within the cerebral hemispheres called the lateral ventricles. They both connect with the third ventricle through a separate opening called the foramen of Monro. The third ventricle connects with the fourth ventricle through a long narrow tube called the aqueduct of Sylvius. ***(****Snell, Richard S. 2010****)*** **.**From the fourth ventricle,

CSF flows into the subarachnoid space where it bathes and cushions the brain. CSF is recycled (or absorbed) by special structures in the superior sagittal sinus called arachnoid villi.A balance is maintained between the amount of CSF that is absorbed and the amount that is produced. A disruption or blockage in the system can cause a buildup of CSF, which can cause enlargement of the ventricles (hydrocephalus) or cause a collection of fluid in the spinal cord (syringomyelia).CSF fluid circulates inside the brain and spinal cord and then outside to the subarachnoid space.*(Tamraz,et al2006).*

2.3 Pathology of brain lesion:

Brain lesion is an area of injury or disease within the brain, there are many types of brain lesions, the major types are traumatic, infection, malignant ,benign, brain cell death or malfunction and ionizing radiation. brain tumors are space-occupying lesions within the cranial cavity. It can be either benign or malignant, some of this tumors is biologically malignant but histologically benign, it is so difficult to remove it.

2.3.1 Etiology of brain tumors:

Although a number of chemical and viral agents can cause brain tumors in laboratory animals, there is no evidence that these agents directly cause brain cancer in humans. Cranial irradiation and exposure to some chemicals may lead to an increased incidence of astrocytomas and meningiomas. There may also be a hereditary factor, 16% of persons with primary brain tumors have a family history of cancer. Childhood tumors are considered to be developmental in origin.(GeorgianneH. and Porth, 2015)

2.3.2 The Clinical manifestations of brain tumors:

Intracranial tumors give rise to focal disturbances because of brain compression, tumor infiltration, disturbance in blood flow, and brain edema.(GeorgianneH. and Porth, 2015).Tumors may be located intra axially (i.e. within brain tissue) or extra axially (i.e. outside brain tissue). Disturbances in brain function are generally greatest with fast growing, infiltrative, intra axial tumors because of

compression, infiltration, and necrosis of brain tissue. Extra axial tumors, such as meningiomas, may reach a large size without producing signs and symptoms cysts may forms within tumors and contribute to brain compression. (GeorgianneH. and Porth, 2015)

Cerebral edema IS usually of the vasogonic type, which develops around brain tumors and is characterized by increased brain water and expand extra cellar fluid. (GeorgianneH. and Porth, 2015), Because the volume of the intracranial cavity is fixed, brain tumors cause a generalized increase in ICP when they reach sufficient size. Tumors can obstruct the flow of CSF in the ventricular cavities and produce hydrocephalic dilatation of the proximal ventricles and atrophy of the cerebral hemispheres complete compensation of ventricular volumes can occur with very slow-growing tumors, but with rapidly growing tumors, increased ICP is an early sign. Depending on the location of the tumor, brain displacement and herniation of the uncus or cerebellum may occur. The clinical manifestation of brain tumors depend on the size and location of the tumor. General signs and sympotoms include headache, nausea, vomiting, mental changes, papilledema, visual disturbances, alterations in sensory and motor function, and seizures.(KOWALCZYK, 2013).The headache that accompanies brain tumors results from compression or distortion of pain-sensitive dural or vascular · structures. It may be felt on the same side of the head as the tumor but is more commonly diffuse in nature.(KOWALCZYK, 2013) Vomiting occurs with or without preceding nausea and is a common symptom of increased ICP and brain stem compression. The vomiting is stimulated by the center, which is located in the medulla oblongata. Vomiting caused by brain tumor is usually unrelated to meals and is often associated with headache. Papilledema results from increased ICP and obstruction of the CSF path ways. It is associated with decreased visual acuity, diplopia and deficits in the visual field.(KOWALCZYK, 2013)Focal signs and symptoms are determined by the location of the tumor, tumors arising in the frontal lobe may

grow to large size, increase the ICP, and cause signs of generalized brain dysfunction before focal sings are recognized. Tumors that impinge on the visual system caused visual loss or visual field defect long before generalized signs develop. Temporal lobe tumors often produce seizures as their first symptom, hallucinations of smell or hearing. Brain stem tumors commonly produce upper and lower motoneuron sings, such as weakness of facial muscles. Cerebellar tumors often cause ataxia of gait (GeorgianneH. and Porth, 2015)

2.3.3 Types of brain tumors

Tumors of the neruoglia like: Astrocytoma, Glioblastoma multiform ,brainstem glioma, ependymoma, oligodendroglioma and mixed gliomas.

Tumors of neural cells like: .Neuroblastoma, medulloblastoma. Tumors of non-neural tissue like Meningioma, pineal tumors, pituitary tumors, cranipharyngiomas and Metastatic Tumors

2.3.4 Tumors of the neruoglia like:

2.3.4.1 Gliomas:-

Gilomas are the commonest type of intracranial tumors, are derived from primary neuroglial tissue containing microglia, oligodendrocytes, ependyma and astrocyte or from neuronal cells. Some tumors may contain different types of cells in it, and classified as: *Low-grade Tumors:* these have a low celluarity, no mitoses, no nuclear peomorphism, no vascular endothelial proliferation and no necrosis. *High-grade anaplastic Tumors:* these have high celluarity, nuclear pleomorphism, and vascular endothelial proliferation. Necrosi in a glial tumor is an index of a high degree of malignancy.(Singh, 2015).

2.3.4.2. Astrocytoma:

The tumor arises from star-shaped glial cells called astrocytes. It can be any grade. In adults, an astrocytoma most often arises in the cerebrum and appear as ill defined pale areas of softening in the tissue of the nervous system, which blend into adjacent normal brain. They may arise in the cerebral hemispheres, tumor is gray-white infiltrative, that expand and distort the underlying brain.

These tumors may arise in adult life as well as in childhood, most of it present with focal neurological signs or those of raised intra cranial pressure. Because of the ill-defined nature of most astrocytomas, surgical removal is rarely possible and treatment by surgical debulking and radiotherapy is usual,Grade I or II astrocytomaIt may be called a low-grade glioma, it is possible for low-grade tumor to evolve into high-grade tumor with time. Tumors do not metastasize but recur locally and by spread within the brain substance.(Laggner *et al.*, 2007).

2.3.4.3 Anaplastic-malignant astrocytoma:

Is derived from astrocytic cell, are dot grossly distinguishable from astocytomas and appear as ill-defined pale areas of softening in the tissue of the nervous system which bland into adjacent normal brain. They most commonly arise in the cerebral hemisphere and less commonly in the brain stem, cerebellum or spinal cord. Grade IIIastrocytomait's sometimes called a high-grade or an anaplastic astrocytoma.(Laggner *et al.*, 2007)

2.3.4.4 Glioblastoma multiform:

They generally arise in the cerebral hemisphere, less frequently in the brain stem and only very rarely in the cerebellum or spinal cord. It is most commonly affect elderly (40-60 year).They can be distinguished from the other astrocytomas by its variegated appearance, hence the designation " multiform" some regions may be white and firm, others yellow and soft, and foci of necrosis, cysts, and hemorrhages are often seen. (GeorgianneH. and Porth, 2015)The glioblastoma multiform IS commonly used as a synonym for highly malignant forms of astrocytomas (Grade III or Grade IVastrocytoma**,** It may be called a glioblastoma or malignant astrocytic glioma.*).* It is the most frequent brain tumor, accounting for 12–15% of all intracranial tumors. GBM may manifest at any age, but about 80% of patients are between 45 and 80 years old. It may develop from diffuse astrocytomas, anaplastic astrocytomas, but more frequently they occurred after a short clinical history. Primary GBM accounts

for the vast majority of cases in older people, while secondary GBM typically develops in younger patients (less than 45 years)**.** The prognosis for patients with glioblastoma is very poor with current treatment comprising resection when feasible together with radiotherapy and chemotherapy, the mean length of survival after diagnosis is only 8 to 10 months, with fewer than 10% of patients alive after 2 years survival. Is substantially shorter in older patients.(Laggner *et al.*, 2007).

2.3.4.5 Pilocytic astrocytoma

A tumors derived from astrocytic cells which histologically have abipolar spindle-shaped morphology hence hair-like or pilocytic. Are distinguished from other strocytoma by a distinctive pathologic appearance and their almost invariably benign biologic behavior. Typically, they occur in children and young adults and are usually located in the cerebellum, but they are also found in the floor and walls of the third ventricle, the optic chiasm and nerves, and, occasionally, in the cerebral hemispheres. These tumors often manifest as a mural nodule in the wall of cyst but, if solid, may be well circumscribed or apparently infiltrative. These tumors are extremely slow growing and have the best prognosis of all brain tumors, patients have survived more than 40 years after complete resection but if the tumors site is critical brain area, the survival rate is low 5-3 years(Laggner *et al.*, 2007)

2.3.4.6 Brain stem gliomas

The tumor occurs in the lowest part of the brain. It can be a low-grade or high-grade tumor. The most common type is diffuse intrinsic pontine glioma. occurring mostly in the first two decades of life and compose about 20 % of primary brain tumors in this age group. Histologically, they resemble the astrocytomas in the hemispheres; about 50% prove to be glioblastoma. With current radiotherapy the five year survival rate for the composite group is between 25 and 40%(Laggner *et al.*, 2007)

2.3.4.7. Oligodendroglioma:

These is glial tumors, the tumor arises from cells that make the fatty substance that covers and protects nerves, It can be grade II or III. comprise about 5% gliomas-they are most frequent in middle life, are found mostly in the cerebral hemispheres and have only rarely been described in the brain stem, cerebellum or spinal cord. The temporal lobe is a frequent site of occurrence. They are well-circumscribed, gelatinous gray massed, often with cysts, focal hemorrral1ages and calcifications, the calcification is often available radiologic diagnostic clue. As with other gliomas there is occasionally extension of tumors in to the subarachnoid space and dissemination through the CSF.(Laggner *et al.*, 2007)

2.3.4.8. Ependymoma:

Are derived from the single layer of epithelium that lies the ventricle and extend down the center of the spinal cord as the remnant of the central canal. Although they may occur at any age and anywhere in this epithelium, they are particularly like to occur in the first two decades of life in the fourth ventricle, they constitute between 5 and 10% of primary brain tumors of this age group. In middle life, the spinal cord is their most likely site of occurrence. Clinically, posterior fossa ependymomas often manifest with hydrocephalus secondary to progressive obstruction of the fourth ventricle rather than invasion of the pons or medulla-prognosis is poor despite the slow growth of the tumor and the usual lack of histologic evidence of anaplasia. Because of their relationship to the ventricular system, CSF dissemination is a common finding. It’s most commonly found in children and young adults, it can be grade I, II, or III, an average survival of about 4 years following surgery and radiotherapy has been reported(Sataloff, et al, 2015)

2.3.4.9 Pediatric Brain Tumors:

Brain tumors in children typically come from different tissues than those affecting adults. Treatments that are fairly well-tolerated by the adult brain (such as radiation therapy) may prevent normal development of a child's brain,

especially in children younger than age five. According to the Pediatric Brain Tumor Foundation, approximately 4,200 children are diagnosed with a brain tumor in the U.S. Seventy-two percent of children diagnosed with a brain tumor are younger than age 15. In some patients the descended cerebellar components are debunked or removed. Some types of brain tumors are more common in children than in adults. The most common types of pediatric tumors are Medulloblastomas, low-grade astrocytomas (pilocytic), ependymomas, Dysembryoplastic neuro epithelial tumor (DNET),craniopharyngiomas and brainstem gliomas (Tobin et al 2015).

2.3.4.9.1 Dysembryoplastic neuro epithelial tumor (DNET):

Dysembryoplastic neuro epithelial tumor (DNET) is a recently described, morphologically unique, and surgically curable low-grade brain tumor which is included in the latest WHO classification as neuronal and mixed neuronal glial tumor. It is usually seen in children and young adults. The importance of this particular entity is that it is a surgically curable Neuro epithelial neoplasm. When recognized, the need for adjuvant radiotherapy and chemotherapy is obviated. We hereby present a case report of an 8years old male child who presented with intractable seizures and parieto occipital space occupying lesion. Histological, the tumor exhibited features of WHO grade I dysembryoplastic neuro epithelial tumor which was further confirmed by immunohisto chemistry (Sukheeja and Mehta, 2016).

2.3.5. Tumors of the Meanings: **Meningiomas**

Meningiomas are predominantly benign tumors of adult. They arise from the meningothelial cells of the arachnid although they are most intimately associated with the dura. They comprise about 20% of primary brain tumors and generally have their onset in the middle or later years of life and are more frequent in women (3:2 ratio of woman to men), are un common in the pediatric population. Meningioma is slow growing, well-circumscribed and often highly vascular tumors, they are usually benign, and complete removal is possible if

the tumor does not involve vital structures. In meningioma calcification is visible in approximately 20% of the lesions(KOWALCZYK, 2013). Common sites of tumors include the Para sagittal aspect of convexity, dura over the lateral convexity, the sella turcica, and the foramen magnum. Malignant meningioma is rapidly growing expansible lesions, which mainly compress but also invade underling brain. It can be grade I, II, or II I; it's usually benign (grade I) and grows slowly. They have highly typical histological features and behave as locally aggressive malignant tumors resembling sarcomas. Surgical removal is the method of treatment but may recur after total removal.(Laggner, *et al*, 2007)

2.3.6 Metastatic tumor:

Secondary metastases from another site can involve any intracranial structure and account for about 25% of all brain tumors. Brain metastasis usually arises from lung carcinoma; other significant causes include breast cancer, colon cancer, and malignant melanoma. Signs and symptoms of brain metastasis are similar to those for other brain tumors. Patients with metastases form other sites usually present with signs of increased intracranial pressure, especially headache and ataxia. Solitary metastases are unusual typically, they are multiple, well-circumscribed, roughly spherical masses of varying size that are usually located at the junction of the gray and white matter and are surrounded by zones of edematous white matter. Necrosis, cyst formation, and hemorrhage are frequent. Carcinomatous meningitis, with large numbers of tumor nodules studding the surface of the brain, cord, and intra dural nerve roots, is an occasional complication that is particularly associated with small cell carcinomas and adenocarcinomas of the lung and carcinoma of the breast. Treatments of it including surgical resection of a single brain metastasis, if possible, radiotherapy have been found to be helpful in some instance. Chemotherapy is performed, but the prognosis is generally quite poor (Sataloff, et al, 2015)

2.3.7 Brain abscess:

A focal area of infection within the cerebrum or cerebellum presents as an expanding mass lesion. Penetration wound of the skull usually with a staphylococci secondary infection and fungi. Direct spread: an infected middle ear or mastoid spreading to either the temporal lobe or the cerebellum. Blood spread specific embolus from lung focus of infection like lung abscess ,CT and MRl and provide accurate diagnosis and localization of the abscess typically appearing as a ring enhancing after injection of contrast media with extensive edema, MRS has been proven beneficial in differentiating between brain abscesses and other cystic lesion(Lai , et al, 2002)

2.3.8 Tuberculoma

Tubercle bacilli cause chronic caseating intra cranial granulomas. Tuberculomas which are the commonest single intra cranial masses in areas such as India. Where tuberculosis is common. Tuberculomas either present as mass tensions or occur in the course of tuberculoses meningitis. They may also be symptom less and appear on skull x-ray as areas of intra cranial calcification. The symptoms of it is headache, focal signs (aphasia) ,epilepsy and raised ICP. The presentation may thus be remarkably similar to many cerebral neoplasm. (Monteiro *et al.*, 2013)

2.4 Magnetic Resonance Spectroscopy MRS:

Early and accurate diagnosis of patients with cerebral demyelinating or infection diseases, space occupying mass lesions and neurological deficits, is essential for optimum treatment decision concerning the administration of specific medication or chemotherapeutic agents, radiation therapy and/or surgical resection. Currently, conventional MR imaging (MRI) is considered to be an established and useful tool in brain disease detection and it is widely chosen as the initial examination step in patients suspected of brain lesions as it is effective in simultaneously characterizing the soft tissue, cerebro spinal fluid (CSF) spaces, and blood vessels. It is a flexible imaging modality for which

contrast can be extensively manipulated without patient burdening by ionizing radiation. Nevertheless, the accurate characterization of brain lesions with MR imaging remains problematic in several cases as the sensitivity and specificity with which this modality defines several brain lesions remains limited

To overcome the aforementioned limitation, the development of new imaging techniques is required, in order to highlight functional or metabolic properties of brain tissue. Proton Magnetic resonance spectroscopy (1H-MRS) is one such technique which provides a non invasive method for characterizing the cellular biochemistry which underlies brain pathologies, as well as for monitoring the biochemical changes after treatment in vivo. It is considered as a bridge between metabolism and the anatomic and physiological studies available from MRI. Until now, H-MRS has been used as both a research and a clinical tool for detecting abnormalities -visible or not yet visible- on conventional MRI. (Nelson ,2003)

H-MRS has been always challenging in terms of its technical requisites (field strength, gradients, coils and software), as well as the accurate metabolic interpretation with regards to pathologic processes. However, the clinical applications of 1H-MRS are continuously increasing as the clinical hardware have become more robust and user-friendly along with improved data analysis, spectra post-processing techniques and metabolite interpretation confidence. H-MRS in terms of its clinical usefulness as well as its technical prerequisites. (Nelson ,2003)

2.4-1 Basic principles

In order to introduce the basic concepts and terminology of 1H -MRS, the basic principles of MRS are briefly described below. Proton is a charged particle with spin, and exhibits the electromagnetic properties of a dipole magnet. When protons are placed in an external magnetic field B**0**, they align themselves along the direction of the field (either parallel or anti-parallel) and demonstrate a circular oscillation. The frequency of this circular motion (called Larmor

frequency) is dependent on the strength of the local magnetic field and the molecular structures at which protons belong. This can be expressed by the Larmor equation: $\omega = \gamma B_0$ where ω_0 is the Larmor frequency, γ is the gyromagnetic ratio specific for the nuclei, and B_0 is the strength of the external magnetic field. When electromagnetic energy (in the form of a RF pulse) is supplied at this frequency, the molecules absorb this energy and change their alignment. When the RF pulse is switched off, the molecules realign themselves to the magnetic field by releasing their absorbed energy. This released energy is the basis of the MR signal . H-MRS uses the same hardware as conventional MRI, however, their main difference is that the frequency of the MR signal is used to encode different types of information. MRI generates structural images, whereas H-MRS provides chemical information about the tissue under study. Although recent studies have shown promise for the use of H-MRS to investigate malignant processes to prostate , breast , skeletal muscles , cervical and ovarian cancer , the overwhelming number of applications have been demonstrated in the brain, due to the absence of free lipid signals in normal cerebrum, relative ease of shimming, and lack of inherent motion artifacts .(Soares ,2009)

The output of H-MRS is a spectrum which is described by two axes as it is illustrated in . The vertical axis (y) represents the signal intensity or relative concentration for the various cerebral metabolites and the horizontal axis (x) serves to describe the frequency chemical shift in parts per million (ppm). The nature of the chemical shift effect is to produce a change in the resonant frequency for nuclei of the same type attached to different chemical species. It is due to variations in surrounding electron clouds of neighboring atoms, which shield nuclei from the main magnetic field (B0). The resulting frequency difference can be used to identify the presence of important chemical compounds show figure (2.8). Within the spectrum, metabolites are characterized by one or more peaks with a certain resonance frequency, line

width (full width at half maximum of the peak's height, FWHM), line shape (e.g., lorentzian or Gaussian), phase, and peak area according to the number of protons that contribute to the observed signal.(Soares ,2009)

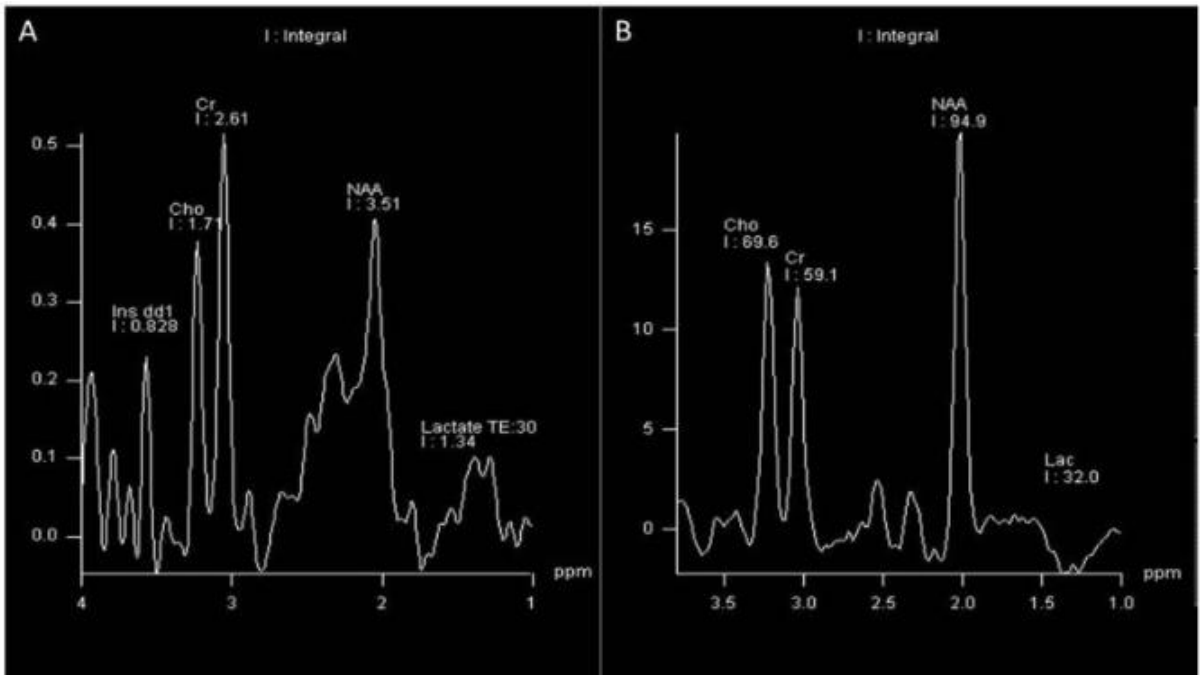

Figure 2. 8 Spectrum obtained with TE = 30ms (A) and TE = 135ms (B). Note the inverted lactate peak (doublet) with long TE acquisition and the more number of sharps resonance with short TE. Cho– choline; Cr- creatine NAA– N-acetyl aspartate; and myo-inositol .(Soares ,2009**).**

2-4-2. Neurospectroscopy biochemical features and their clinical significance

Accurate classification of cerebral lesions by in-vivo H-MRS requires determination of the relationship between metabolic profile and pathologic processes. (Soares ,2009)

2-4-2-1 N-Acetyl Aspartate (NAA)

In H-MR spectra of normal cerebral tissue, is the most prominent resonance which originates from the methyl group of NAA at 2.01ppm with a contribution from neurotransmitter N-aspartyl-glutamate (NAAG) . NAA is exclusively localized in central and peripheral nervous system and it is synthesized in brain

mitochondria. Its concentration subtly varies in different parts of the brain and undergoes large developmental changes, increasing from 4.82mM at birth to 8.89mM in adulthood. Although NAA is considered as a neuronal marker and equate with neuronal density and viability, its exact function remains largely unknown. The utility of NAA, as an axonal marker is supported by the loss of NAA in many white matter diseases, including leukodystrophies , multiple sclerosis (MS) and hypoxic encephalopathy , chronic stages of stoke and tumors . However, there are cases when the abnormal levels of NAA do not reflect changes in neuronal density, but rather a perturbation of the synthetic and degradation pathways of NAA metabolism. For instance, in Canavan's disease high levels of intracellular NAA are due to aspartoacylase (ASPA) deficiency, which is the enzyme that degrades NAA to acetate and aspartate. Further examples that show the lack of direct relationship of NAA to neuronal integrity include various pathologies such as temporal lobe epilepsy (TLE) or amyotrophic lateral sclerosis (ALS) , which exhibit spontaneous or treatment reversals of NAA to normal levels. (Soares ,2009)

2-4-2-2 Choline-containing compounds Comprise signals from free choline (Cho), phosphocholine (PC) and glycerophosphocholine (GPC), with a resonant peak located at 3.22 ppm. Since the resonance contains contributions from several methyl proton choline-containing compounds, it is often referred as "total Choline" (tCho). tCho is involved in pathways of phospholipids' synthesis and degradation thus reflecting a metabolic index of membrane density and integrity as well as membrane turnover Consistent changes of tCho signal have been observed in a large number of cerebral diseases. Processes that lead to elevation of tCho include accelerated membrane synthesis of rapidly dividing cancer cells in brain tumors , cerebral infractions, infectious diseases and inflammatory-demyelinating diseases . Unlike to NAA, which is distributed almost homogeneously throughout the healthy brain, tCho exhibits a marked regional variability with higher concentrations observed in the pons and lower

levels in the vermis and dentate. Therefore, detailed knowledge about regional variations of tCho is necessary for an accurate interpretation of the metabolite's levels, especially in diseases such as epilepsy and psychiatric disorders where tCho is subtly different to normal levels. (Moller ,2002).

2-4-2-3 Creatine (Cr) and Phospho creatine (PCr)

Cr and PCr arise from the methyl and methylene protons of Cr and phosphorylated Cr. Within the H-MR spectrum, tCr is located at 3.03 ppm and 3.93 ppm resonant frequencies. In the brain tCr is present in both neuronal and glial cells and is involved in energy metabolism serving as an energy buffer via the creatine kinase reaction retaining constant ATP levels and as an energy shuttle, diffusing from the energy producing (i.e. mitochondria) to energy utilizing sites (i.e. nerve terminals in brain) .As tCr is not naturally produced in the brain, its concentration is assumed to be stable with no changes reported with age or a variety of diseases and is used for calculating metabolite ratios (NAA/Cr, tCho/Cr etc) .Nevertheless, the use of tCr as an internal concentration reference should be used with caution as decreased tCr levels have been observed in the chronic phases of many pathologies including tumors , stroke and gliosis . (Jonathan ,2004)

2-4-2-4 Myo-inositol (mI):

Is a cyclic sugar alcohol that gives rise to four groups of resonances with the larger and most important signal occurring at 3.56 ppm. It is observable on short time echo (TE) spectra as it exhibits short T2relaxation times and is susceptible to dephasing effects due to J-coupling. The exact function of mI is uncertain, however it has been proposed as a glial marker and an increase of mI levels is believed to represent glial proliferation or an increase in glial cell size, both of which may occur in inflammation. Additionally, this metabolite is involved in the activation of protein C kinase which leads to production of proteolytic enzymes found in malignant and aggressive cerebral tumors, serving as a possible index for glioma grading. (Moller ,2002).

2-4-2-5 Lactate and Lipids:

In the normal brain should be maintained below or at the limit of detect ability within the H-MR spectrum, overlapping with macromolecule (MM) resonances at 1.33ppm (doublet) and 0.9-1.3 ppm respectively. Any detectable increase in lactate and lipids can therefore be considered abnormal. Lactate is present in both intracellular and extracellular spaces and provides an index of metabolic rate and clearance . As an end-product of anaerobic glycolysis, increased lactate levels have been observed in a wide variety of conditions in which oxygen supply is restricted such as in both acute and chronic ischemia , metabolic disorders , and tumors]. Lactate also accumulates in tissues that have poor washout like cysts and normal pressure hydrocephalus . However, in CSF, lactate may be detectable at low levels in normal subjects with prominent ventricles . The spectral region between 0.9ppm and 1.3ppm as referred above; represents the methylene (1.3ppm) and the methyl (0.9ppm) groups of fatty acids. It is during membrane breakdown when fractured proteins and lipid layers become visible. (Jonathan ,2004)

2-4-2-6 Glutamate (Glu) and Glutamine (Gln)

Together they form a complex of peaks (Glx complex) between 2.15 ppm and 2.45 ppm, as their similar chemical structures, renders their distinction difficult within a proton spectra at 1.5T. However, at 3T and above Glu and Gln start to become resolved and at magnetic fields of 7T and higher, the Glu and Gln resonances are visually separated leading to big quantification accuracy. Glu is the major excitatory neurotransmitter in mammalian brain and the direct precursor for the major inhibitory neurotransmitter, γ-aminobutyric acid (GABA). The amino acid Gln, is an important component of intermediary metabolism, is primarily located in astroglia and it is synthesized from Glu. The Glx complex plays a role in detoxification and regulation of neurotransmitters. Increased levels of Glx complex are markers of epileptogenic processes and low levels of Glx have been observed in Alzheimer Dementia and patients with

chronic Schizophrenia. Glx complex increment, has been also observed in the peritumoral brain edema correlated with neuronal loss and demyelination. Glx might be used as an in vivo index of inflammation since they observed elevated Glx levels in acute MS plaques but not in chronic ones. (Bonekamp ,2011)

2-4-2-7Alanine (Ala)

Is an amino acid present in the normal brain, resonating at 1.47 ppm. It is frequently considered as a specific metabolic characteristic of meningiomas, however, its identification rate varies from 32% to 100% . It can be also presented in neurocytomas gliomas and PNETs. In vivo H-MRS at 1.5T often cannot provide a distinction between Ala and Lac peaks as they resonate in neighboring frequencies. When both metabolites are present they produce a triplet peak located between 1.3 ppm and 1.5 ppm observed at 3T and higher. (Bonekamp ,2011)

2-4-2-8 Glycine (Gly)

Is the simplest amino acid and possible antioxidant, distributing mainly in astrocytes and glycinergic neurons, where it is regulated due to its neuroactive properties as an inhibitory neurotransmitter . It resonates at 3.55 ppm and it overlaps with mI rendering the observation of Gly impossible in a non-processed spectrum. In cases of mI absence, the even low Gly levels can be quantified . High levels of Gly have been observed in glioblastomas, medulloblastomas, ependymomas and neurocytomas. It has also been reported that this metabolite may provide a noticeable metabolic index for the differentiation of glioblastomas from lower grade astrocytomas, primary gliomas from recurrence and glial tumors from metastatic brain tumors . (Jonathan ,2004)

2-4-2-9Taurine (Tau) :

Gives two triplets at 3.25 ppm and 3.42 ppm, which can be observed at higher magnetic fields as they significantly overlap with Cho and mI. Tau is an inhibitory neurotransmitter that activates GABA-a receptors or strychnine-

sensitive glycine receptors and it has also been proposed as an osmoregulator and a modulator of neurotransmitter action. High levels of Tau have been observed in medulloblastoma, pituitary adenoma and metastatic renal cell carcinoma . Shirayama et al have been also reported increased levels of Tau in the medial prefrontal cortex in schizophrenic patients . (Jonathan , 2004)

2-4-2-10 Glutathione (GSH):

Is the major protective molecule of living cells assigned to 2.9 ppm. It serves as an antioxidant and detoxifier thus having an important role against oxidative stress . Glutathione also plays a role in apoptosis and amino acid transport . Altered levels of this metabolite have been reported in acute ischemic stroke patients as ischemia is associated with significant oxidative stress , in Parkinson's disease and other Proton Magnetic Resonance Spectroscopy of the Central Nervous System . neurodegenerative diseases affecting the basal ganglia. GSH has been also found to be significantly elevated in meningiomas when compared to other tumors , showing as well an inverse relationship with glioma malignancy. (Jonathan ,2004)

2-4-2-11 Several other amino Acids

Such as Succinate at 2.4 ppm, Acetate at 1.92 ppm, Valine and Leucine at 0.9 ppm together with Alanine and Lactate, are the major spectral findings of bacterial and parasitic diseases. Acetate and Succinate are presumably originating from enhanced glycolysis of the bacterial organism . The amino acids Valine and Leukine are known to be the end-products of proteolysis by enzymes released in pus . Specifically, Leucine and Valine peaks have been detected in cystercercosis lesions, however they have not been reported in proton MR spectra of brain tumors. (Jonathan ,2004)

2-4-3 Technical considerations

In order to precisely identify the metabolite peaks within a spectrum, several technical considerations should be taken into account concerning the applied magnetic field, the shimming procedures as well as the adequate voxel

positioning and the available H-MRS techniques , which all highly affect the quality of the yielded spectrum before any post processing intervention. (Bonekamp ,2011)

2-4-3-1 Field strength

In H-MRS clinical applications, it is not the signals of water and fat that are of interest, but rather the smaller signals of metabolites, thus a magnetic field of sufficient strength is required. Therefore, most clinical 1H-MRS measurements are performed using MR systems with field strengths of 1.5T and higher. Although more powerful 4, 6, 7 , and even 8T MR body scanners are currently in use, the most common high field systems operate at 3T. The main advantage of increasing magnetic field strength is the subsequent increase of the signal-to-noise ratio (SNR). Theoretically, SNR increases proportionally to field strength, however, when put into clinical practice, the study of Barker et al, demonstrated a 28% increase in SNR at 3T compared to that of 1.5T at short TEs, appreciably less than the theoretical 100% improvement. Another advantage of magnetic field increment, is the proportional increase of the Chemical Shift, from 220 Hz at 1.5T to 440 Hz at 3T. This is reflected by more effective water suppression and improved baseline separation of J coupled metabolites such as glutamate, glutamine and GABA, without the need of sophisticated spectral editing techniques . The improvement in spectral resolution is further evident at 7T where weakly represented neuro chemicals with important clinical impact, such as scyllo-Ins, aspartate, taurine and NAAG, can be clearly visible.
(Bonekamp ,2011)

On the other hand, the aforementioned advantages may be hampered by intrinsic field dependent technical difficulties that should be considered. When the frequency shift between two adjacent nuclei is large enough, a measurable alteration of MR signal, used to encode the x- and y-axis spatial coordinates, will occur producing a spatial misregistration. This means that the volume of MRS information may not be the same as that displayed on the localizer MR

image. Encountered at high magnetic fields. The large separation of coupled resonances such as Lactate can result in incomplete inversion of the coupled spin over a large portion of the selected volume, resulting in anomalous intensity losses at long echo times. Strategies to quantify the lactate signal loss have been previously discussed by Lange et al. Magnetic susceptibility from paramagnetic substances and blood products, are sensibly increased with increasing magnetic field strength. Consequently, magnetic field in homogeneity and susceptibility artifacts makes more difficult to obtain good-quality spectra, especially from largely heterogeneous lesions. Improved local shimming methods can alleviate the problem. (Bonekamp, 2011)

2-4-3-2 Shimming

Shimming refers to the process of adjusting field gradients, either manually or automatically, in order to optimize the magnetic field homogeneity over the volume under study. Magnetic field in homogeneities result primarily from susceptibility differences between different tissues and between tissue and air cavities, which are scaled non-linearly in ultra-high magnetic fields . Thus, voxels that are placed in inhomogeneous regions of the brain, such as the temporal poles, are difficult to shim due to their close proximity to the sinuses. Field homogeneity is specified by measuring the full width at half maximum (FWHM) of the water resonance, which determines the spectral resolution. Special emphasis, especially when field is increased, must be placed on shimming, as it increases both sensitivity and spectral resolution. This is why most devices come equipped with second or third order shimming by monitoring either the time domain or frequency domain of the 1H-MRS signal. Some times 4-order shimming might be necessary ,especially in cases when field homogeneity should be reached in large volumes of interest during magnetic resonance spectroscopic imaging (MRSI). Effective shimming requires methods for mapping field’s strength variations over the area under study. Methods that have been developed for field mapping can be grouped in

two categories: those which are based on 3D field mapping and those which map the magnetic field along projections .In both shimming methods, information about the magnetic field variation is calculated from phase differences acquired during the evolution of the magnetization in a non-homogeneous field. (Bonekamp, 2011)

2-4.3-3. Voxel positioning

For a meaningful in vivo 1H-MRS, it is important to locate the voxel in the appropriate region for a reliable metabolic characterization of a lesion . First and foremost, cautious spatial localization is used to remove unwanted signals from outside the ROI, like extra cranial lipids and to avoid “partial volume effects”, thereby providing a more genuine tissue characterization. Additional benefits from careful spatial voxel localization, originate from the fact that variations in the main magnetic field and magnetic field gradients, are greatly reduced, thereby providing narrower spectral lines and more uniform proton excitation. Several lesions and stroke infarcts do not always place themselves in positions that are easy to shim such as temporal lobes, the base of the brain and the cortex near the scull. Small voxels is those regions are easier to shim, but the signal also depends on volume so a voxel with 1-cm sides is often considered the practical minimum size to achieve a reasonable SNR. (Kousi, 2012)

2-4.3-4.1H-MR spectroscopy data acquisition techniques

Spectra can be acquired either with a single voxel (SV) technique (single voxel spectroscopy, SVS) or multiple voxels technique, known as either magnetic resonance spectroscopic imaging (MRSI) or chemical shift imaging (CSI) in two or three dimensions. SVS is based on the stimulated echo acquisition mode (STEAM) or the point resolved spectroscopy (PRESS) pulse sequences while MRSI uses a variety of pulse sequences (Spin Echo, PRESS etc.) . SVS acquires a spectrum from a small volume of tissue located at the intersection of three mutual orthogonal slice-selective pulses as depicted. The pulse sequence is

designed to collect only the echo signal from the point where all three slices intersect. (Kousi, 2012)

2-4-3-5 Water and lipid suppression techniques:

Water and pre cranial lipid suppression techniques are of paramount importance in 1HMRS procedure in order to observe the much less concentrated metabolite signals. The metabolites of interest are usually about a factor of 8,000 less in concentration than water. Therefore, the water suppression efficiency should be robust and should not vary spatially across the field of view (FOV). As water and metabolites T1s are sufficiently different, it is possible to suppress the water signal and observe the metabolites in the close proximity to the water resonance . The third method involves the acquisition of two separated scans in which the metabolite resonances are inverted. The large (unsuppressed) water resonance, as well as the water-related sidebands, is not inverted in either scan. The difference between the two scans therefore results in a water-subtracted (suppressed) metabolite spectrum without any interfering water-related sidebands . Lipid suppression can be performed by avoid the excitement of the lipid signal using STEAM or PRESS localization to select a relatively large rectangular volume inside the brain. Since the extra cranial lipids are not excited they do not contribute to the detected signal. Opposite to the strategy employed by volume pre-localization, outer volume suppression pulses (OVS) are applied to pre saturate the lipid signal . As illustrated in , rather than avoiding the spatial selection of lipids, OVS excites narrow slices centered the brain's lipid-rich regions. Additionally, the difference in T1s of lipids (250-350 msec) and metabolites (1000-2000msec) allows the application of an inversion pulse (inversion time ~ 200 msec), which will selectively null the lipid signal. By choosing the inversion delay such that the longitudinal lipid magnetization is zero, the lipids are effectively not excited. (Bonekamp, 2011)

2-4-3-6 Post processing techniques

In MR spectroscopy, post-processing is considered any signal manipulation performed in order to improve the visual appearance of the MR spectrum or the accuracy during metabolite estimation. Therefore, for a reliable analysis of in vivo 1H-MR spectra, an understanding of the principles of post-processing techniques is necessary. Signal post-processing can be performed either on time domain or after Fourier transformation on frequency domain. Special functions, called filters, can be subsequently applied at the signal in the time domain. The goal is to enhance or suppress different parts of the FID leading to improved signal quality. The three most commonly used filtering approaches are: sensitivity enhancement, to reduce the noise from the FID; resolution enhancement, to achieve narrower metabolite line widths; and apodization for signal's ripple (due to signal truncation) reduction . The FID of a spectrum, when acquired, is sampled by the analog-to-digital converter over N points in accordance to the nyquist sampling frequency. Therefore, if the number of points is not sufficient, the reliable representation of the signal fails. Instead of increasing the acquisition time with the inevitable noise increment, the acquired FID can artificially be extended by adding a string of points with zero amplitude to the FID prior to Fourier Transformation, a process known as zero filling. Zero filling does not increase the information content of the data but it can greatly improve the digital resolution of the spectrum and helps to improve the spectral appearance , rendering it an important post processing step. After Fourier transformation, the spectrum will be phase corrected. When the zero-phased FID signal shifts to the frequency domain, yields a complex spectrum with absorption (real) and dispersion (imaginary) Lorentz peaks. However, when the initial phase is non-zero, it is not attainable to restore pure absorption or dispersion line shapes and phase correction must be applied . A zero-order phase correction compensates for any mismatch between the quadrature receive channels and the excitation channels to produce the pure absorption spectrum,

whereas, a first-order phase correction compensates for the nuclei dephase due to the delay between excitation and the detection of FID. (Kousi, 2012)

2-4-4 H-MRS metabolic profiles of brain lesions

The effective differential diagnosis of brain lesions using 1H-MRS depends on the ability of the experienced neuroscientist to interpret and evaluate the metabolic criteria and data underlying each disease. However, similarities in the chemical composition among diseases and/or atypical metabolic characteristics, often burden the diagnosis. Thus, a clinical guide to the main MR spectroscopic findings of cerebral disorders is necessary. This section focuses on the metabolic patterns of a variety of intra-cranial diseases. (Kousi, 2012)

2.4.4.1 MRS metabolic criteria of Gliomas

Gliomas are spatially heterogeneous lesions which arise from the 'gluey', or supportive tissue of the brain. The main types of gliomas are astrocytomas, oligodendrogliomas, and ependymomas. 1H-MRS is increasingly used in clinical studies to non-invasively identify regions with metabolic specific characteristics that reflect glioma type and grade. A common observation in 1H-MRS of all glial tumors is a decreased levels of NAA and increased levels of tCho with a significant overlap among different glioma types . Thus, 1H-MRS is currently used primarily to differentiate glial tumor grade rather than to confirm a histopathological diagnosis However, the signal intensity of glutamine and glutamate (Glx) may aid the distinction between oligodendrogliomas and astrocytomas. found significantly increased Glx levels for oligodendrogliomas when compared to that of astrocytomasusing short TE 1H-MRS. Additionally, in a study by Majos et al, ependymomas differentiated well from the other glial tumors by showing prominent peaks of mI +Gly and Taurine at long TE spectra . Discrimination between tumor grades in gliomas is an important clinical issue, because there is a dispute on the optimum treatment strategy for patients with low-grade tumors. It remains an open question whether 1H-MRS is able to define WHO grade of gliomas. However, a recent

study by Porto et al. revealed a more prominent loss of NAA and increase of tCho in WHO III over WHO II astrocytomas (table 2.3). They consequently proposed NAA/tCho ratio as the most accurate index to discriminate between those tumor grades which is in agreement with what it is generally accepted, i.e. NAA/tCho ratios decrease with higher histological grade of gliomas. Law et al. demonstrated a threshold value of 1.6 for tCho/NAA which provided 74.2% sensitivity and 62.5% specificity in predicting the presence of a high-grade glioma. Thus it is obvious that there is a consistent correlation between Cho increase as well as NAA decrease and tumor grade. A study by Moller-Hartmann et al. revealed that instead of tCho, the amount of lipids proved to be the second-best discriminator between low- and high-grade gliomas, with glioblastomas multiform (GBM) to exhibit the highest amount of lipids since necrosis is one of their microscopic hallmarks. Although it has been previously proved that lactate also increases with grade, it is not always significantly differentiated between high and low grade gliomas . Poor correlation between tumor grade and lactate is most likely due to the difficulty of accurately quantifying lactate in the presence of high lipid signals. Short TE studies have also shown that mI levels may aid tumor classification and grading . Specifically, Castillo et al. retrospectively studied 34 patients with astrocytomas and found a trend towards lower mI levels in high-grade compared with low-grade tumors. One of the most interesting results of the study by Server et al. was the elevation in the peritumoral Cho/Cr and Cho/NAA metabolite ratios in relation to glioma grading. Thereby, as gliomas are infiltrating intracerebral tumors, 1H-MRS may allow to readily appreciate their grade in the perifocal region. (Lee, 2010)

2.4.4.2 MRS metabolic criteria of Cerebral metastasis

Cerebral metastases are a common complication of cancer and can affect 20% to 40% of patients who suffer from primary tumors in lung, breast, skin or colon. When a metastatic brain tumor presents as a solitary lesion, it is usually

indistinguishable from a high grade glioma .Their distinction is important because the treatment approach and follow-up are different for these two different tumors. (Lee, 2010).

The potential of in vivo 1H-MRS for differentiating intracerebral metastases from GBMs has been investigated in a number of studies. Older studies have reported that intra tumoral 1H-MRS, either on short or long TE, was unable to differentiate between metastases and GBMs, as they share common metabolic features. Those concern increased levels of lipids and tCho and reduced levels of NAA Nevertheless, a study by Moller-Hartman et al. revealed elevated lipids for metastases, with statistically significant difference from GBMs. Opstad et al. speculated that the differences in lipid profiles may be related to differences of membrane structures of infiltrative versus migratory tumor cells. Significantly higher Cho/Cr ratio for metastases than for GBMs was reported by Server et al. due to GBMs higher levels of necrosis. (Lee, 2010)

2.4.4.3 Primary Central Nervous System Lymphomas (PCNSL)

Primary central nervous system lymphoma (PCNSL) represents 1% of all brain tumors and its incidence has increased in the last 3 decades. Although densely contrast-enhancing lesions, without the presence of necrosis are characteristic imaging features of PCNS lymphoma, it can be difficult, sometimes even impossible, to distinguish PCNSLs from high grade gliomas on conventional MRI. Their differentiation, however, has important diagnostic and therapeutic implications. (Lee, 2010)

2.4.4.4 MRS metabolic criteria of Gliomatosis Cerebri

Gliomatosis Cerebri (GC) is a rare brain tumor characterized by a diffuse neoplastic overgrowth of glial elements of various histological subtypes (astrocytoma, oligodendroglioma, or mixed glioma) and extensive infiltration of at least two lobes. Unlike gliomas, the neuronal architecture is usually preserved MRI characteristics of GC are non-specific and occasionally it is difficult to differentiate GC from demyelinating diseases or viral encephalitis,

and biopsy is often inconclusive. The WHO classification denotes grades 11,111,1V gliomatosis cerebri Given the unfavorable prognosis of this tumor type, there is a demand for alternative imaging techniques, such as 1H-MRS is used(marked elevation of myo , Cr and Cho level is moderately elevated in gliomatosis cerebri) to grade GC and to detect the most anaplastic areas for determining surgical areas and radio therapeutic targets. (Moller, 2002)

2.4.4.5 MRS metabolic criteria of Radiation necrosis and recurrence

Distinction between radiation necrosis and recurrence of intra parenchyma tumors is necessary to select the appropriate treatment, but it is often difficult based on imaging features alone. We developed an algorithm for analyzing magnetic resonance spectroscopy (MRS) findings and studied its accuracy in differentiation between radiation necrosis and tumor recurrence. (Anbarloui *et al.*, 2015). MRS done to patients with a history of intra parenchyma brain tumor resection and radiotherapy, which had developed new enhancing

Lesion were evaluated by MRS and sub sequently underwent reoperation. Lesions with Choline (Cho)/N -acetyl aspartate (NAA) > 1.8 or Cho/Lipid > 1 were Considered as tumor recurrence and the remaining as radiation necrosis. Finally, pre-operatives MRS diagnoses were compared with histopathological report, Results: The histological diagnosis was recurrence in25 patients and necrosis in 8 patients. Mean Cho/NAA in recurrent tumors was 2.72, but it was 1.46 in radiation necrosis ($P < 0.01$). Furthermore, Cho/Lipid was significantly higher in recurrent tumors ($P < 0.01$) with the mean of 2.78 in recurrent tumors and 0.6 in radiation necrosis. Sensitivity, specificity, and diagnostic accuracy of the algorithm for detecting tumor recurrence were 84%, 75% and 81%, respectively. Conclusion: MRS is a safe and informative tool for differentiating between tumor recurrence and radiation necrosis. (Anbarloui *et al.*, 2015).

2.4.4.6 MRS metabolic criteria of Intracranial abscesses

Brain abscesses are focal, intra cerebral infections that begin with a localized region of cerebritis, evolving into a discrete collection of pus surrounded by a

well-vascularized capsule. The causative organisms involved in brain abscesses are quite variable, and may consist of mixed cultures: aerobes, anaerobes, facultative anaerobes, and facultative anaerobes in combination with aerobes/anaerobes. MRS has been proven beneficial in differentiating between brain abscesses and other cystic lesions , which can be used to implement the appropriate antimicrobial therapy. Brain abscesses reveal specific metabolic substances, such as succinate, acetate, alanine, valine, pyrouvate, leukine, lipids and lactate ,which are all present in untreated bacterial abscesses or soon after the initiation of treatment. Increases in lactate, acetate, and succinate presumably may originate from the enhanced glycolysis and fermentation of the infecting microorganisms. Amino acids such as valine and leucine are known to be the end products of proteolysis by enzymes released by neutrophils in pus . However, cerebral abscesses contain no neurons , therefore no peaks of NAA and Cr/PCr should be detected. The detection of any NAA and/or Cr/PCr is indicative of either signal contamination or erroneous interpretation of acetate peak as NAA . Similarly not Cho peak is present in an abscesses spectrum because there are no membranous structures in its necrotic core . On the other hand, abscesses of tuberculous origin are characterized by the predominant presence of lipids, moderate increase of tCho resonance and no evidence of cytosolic amino acids. Differential diagnosis of brain abscess versus brain tumor is sometimes difficult on the basis of imaging findings and clinical judgment, especially in the case of a brain tumor with a mainly cystic or necrotic component. However, because the vast majority of the aforementioned amino acids have not been detected in brain neoplasms, their presence strongly differentiates abscesses from highly aggressive tumors (Lee, 2010)

2.4.4.7 MRS metabolic criteria of Central Neurocytomas

Central neuro cytomas (CNCs) are a neuronal tumor almost exclusively located in the lateral ventricles that appear in young adults. Most of these tumors do not

recur after surgery and are generally considered benign, with a favorable prognosis, (Moller ,2002)

2.4.4.8 MRS metabolic criteria of Suprasellar tumors:

Pituitary adenomas and craniopharyngiomas, are the most frequent suprasellar space occupying lesions and are generally regarded as benign neoplasms of the pituitary gland. Nevertheless, with respect to the differential diagnosis of suprasellar masses, pituitary adenomas, craniopharyngiomas together with gliomas and meningiomas can be considered. To date only a few cases of pituitary adenomas and craniopharyngiomas have been studied by in-vivo 1H-MRS, probably because of their relative rarity and the technical difficulties in obtaining in vivo high-quality spectra without artifacts is such a region. In a study by Chernov et al., the vast majority of the 19 pituitary adenomas were characterized by a significant reduction of NAA peak, moderate elevation of Cho, and infrequent presence of small lipid and lactate peaks. This metabolic pattern differentiated them from low grade gliomas which showed a moderate decrease of NAA and Cr peaks. In the same study, craniopharyngiomas were typically characterized by a significant decrease of all metabolites and presence of multiple additional peaks which were possibly resulted from the presence of calcifications and microcysts within the investigated volume of tissue. On the contrary, Sener et al. demonstrated very prominent peaks in the craniopharyngiomas between 0.5 and 1.5 ppm, which probably corresponded to lipid peaks. Histological findings also revealed high amounts of cholesterol, lipids and lactate in the cyst fluid correlating with their spectroscopic findings. (Pinker, 2012).

2.4.4.9 MRS metabolic criteria of Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is an auto-immune inflammatory disease of the central nervous system (CNS) in which the myelin sheaths around the axons are damaged leading to demyelination, neuronal affection, inflammation, gliosis and axonal degeneration. 1HMRS is particularly informative in MS, by

providing evidence of the two primary pathologic processes of the disease: active inflammatory demyelination and neuronal injury in both lesional and non-lesional brain tissue. Acute demyelinating lesions reveal increased Cho and Lac resonance intensities due to the release of membrane phospholipids during active myelin breakdown and the impaired metabolism of the inflammatory cells, respectively. Short TE spectra also provide evidence of increased lipids, mI and glutamate levels. Increased glutamate levels in acute MS lesions address a link between the direct axonal injury and glutamate excitotoxicity, whereas mI is suggestive of glial proliferation and astrogliosis. The aforementioned changes are accompanied by a substantial decrease in NAA due to axonal injury reflecting metabolic or structural changes]. It is important to note that the spectroscopic changes seen in acute MS plaques are often very similar to the spectra observed in brain tumors (high Cho, low NAA, increased Lac, etc.), and therefore this should be kept in mind when evaluating spectra from patients with undiagnosed brain lesions. After the acute phase transition, Lac, Cho and lipids seem to return to normal levels, whereas NAA may remain decreased or show partial recovery, lasting for several months. The recovery of NAA can be attributed to resolution of edema, diameter increment of the previously shrinked axons, as a result of the re-myelination and reversible metabolic changes in neurons. There are reports of elevated Cho resonance in chronic MS plaque, probably reflecting the associated gliotic process. Cr seems to be a variable metabolite both in chronic and acute, but is also described to be slowly increasing over time, indicative of gliotic reaction or attempts of incomplete re-myelination of the chronic diseased tissue phases. Metabolic abnormalities in MS patients not only concern the lesions, but are found throughout the normal appearing white matter (NAWM) with notably reduced NAA, which is thought to indicate diffuse axonal dysfunction or loss. It must also be stressed out that the presence of intense gliosis may also cause increased levels of mI and Cr .Increased glutamate, lipids and Cho can be also found in regions of the

NAWM, which later are going to develop T2-hyperintense focal lesions (Lee, 2010)

2.4.4.10 MRS metabolic criteria of Ischemia

Most studies of 1H-MRS of the human brain have focused on the signals from NAA and lactate, as potential markers of brain ischemia, respectively, although there are also often changes in the other metabolite signals, such as Cho, Cr, glutamate (Glu) and glutathione (GSH) . The time course of these metabolite changes through time is an important factor for the diagnosis and prognosis of a brain infarct. (Kousi, 2012)

2.4.4.11 MRS metabolic criteria of Epilepsy

The term epilepsy covers a wide group of syndromes with varied etiology and prognosis. By providing an insight into the biochemical processes related to epileptic seizures, 1H-MRS aids in the localization or lateralization of the epileptogenic foci and in the influence of the metabolites concentration after the administration of antiepileptic drugs and/or after resection of the epileptogenic tissue. (Kousi, 2012)

2.4.4.12 MRS metabolic criteria of Alzheimer/Parkinson diseases

Numerous studies have attempted to identify specific metabolic markers for different neurodegenerative diseases, such as Alzheimer's dementia (AD) and Parkinson's disease (PD), which concern loss of structure or function of neurons including death of the neuronal cells. The clinical objective in that cases is to establish a precise and early diagnosis as well as to understand the related brain changes that could help to slow down the course of the disease (Lee ,2010)

Table(2.2) H-MRS metabolic profiles of brain lesions. (Vermathen P, Administration and (1)H MRS detection of histidine in human brain 2000

marker (metabolite)	ppm	[mM]	indicates	possible to find in...
lipids	0.9-1.2	-	tissue necrosis (highly specific)	brain tumors, abscesses, tissue necrosis
cytosolic amino acids (valine, leucine, and iso-leucine)	0.9	-	products of proteolysis (neutrophil cells)	abscesses, neurocysticerkosis (but not in neoplasms!)
lactate (Lac)	1.2	-	anaerobic glycolysis; inverted double peak (TE136ms)	Balo like MS lesions, malignant tumors, infarcts, abscesses, mitochondrial disorders
alanine (Ala)	1.48	-	inverted double peak (TE 136ms)	meningeomas brain abscesses
acetate	1.5	-	product of propionic acid fermentation and mixed acid fermentation (anaerobic bacteria)	abscesses, neurocysticercosis
N-acetylaspartate (NAA)	2.0	7-17	neurons, axons	decreased in tumors, and any process with tissue destruction
glutamate and glutamine (glx)	2.2-2.7	6-12 and 3-12	excitatory neurotransmitter	increased in stroke, lymphoma, hepatic encephalopathy, metabolic disorders
succinate	2.4	-	product of propionic acid fermentation and mixed acid fermentation	abscesses, neurocysticercosis
Creatine (Cr)	3.0	4.5-10.5	cell energy/ metabolism	mostly stable, used as reference peak
Choline (Cho)	3.2	0.5-3.0	cell membranes (cell turnover, cell destruction)	tumors, lymphomas, stroke, infectious processes, MS
myo-Inositol (mIns)	3.5	4.0-9.0	glucose metabolism mainly in astrocytes	gliosis, hepatic encephalopathy, pontine myelinolysis, MS

2.4.5 World Health Organization (WHO) Brain Tumor Grades

The World Health Organization (WHO) has developed a grading system to Indicate a tumor's malignancy or benignity based on its histological features under a microscope, brain tumors are named based on the type of cell they formed in, and where the tumor first formed in the central nervous system. While the extent or spread of most cancers is usually described in terms of

stages, there is no standard staging system for brain and spinal cord tumors. A tumor is graded based on whether it is slow-growing or fast-growing.

The World Health Organization (WHO) grades tumors (Table 2.3**)** based on how the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Brain tumors are categorized or graded on a scale of I to IV, with I being low-grade (slow-growing) and IV being high-grade (rapidly growing). (**Louis et al. 2016**.)

Grade I (low-grade) the tumor grows slowly, has cells that look a lot like normal cells, and rarely spreads into nearby tissues. Grade I brain tumors may be cured if they are completely removed by surgery. Grade IIthe tumor grows slowly, but may spread into nearby tissue and may recur (come back). Some tumors may become a higher-grade tumor. Grade III the tumor grows quickly, is likely to spread into nearby tissue, infiltrative, and the tumor tend to recur as higher grade. Grade IV (high-grade) the tumor grows and spreads very quickly, mostly malignant. There may be areas of dead cells in the tumor, raid growth, aggressive and necrosis. (**Louis et al. 2016**.)

Table 2.3: World Health Organization (WHO) Brain Tumor Grades (**Louis et al. 2016**.)

	Grade	Characteristics	Tumor Types
Low Grade	WHO Grade I	• Least malignant (benign) • Possibly curable via surgery alone • Non-infiltrative • Long-term survival • Slow growing	• Pilocytic astrocytoma • Craniopharyngioma • Gangliocytoma • Ganglioglioma •
	WHO Grade II	• Relatively slow growing • Somewhat infiltrative • May recur as higher grade	• "Diffuse" Astrocytoma • Pineocytoma • Pure oligodendroglioma •
High Grade	WHO Grade III	• Malignant • Infiltrative • Tend to recur as higher grade	• Anaplastic astrocytoma • Anaplastic ependymoma • Anaplastic oligodendroglioma
	WHO Grade IV	• Most malignant • Raid growth, aggressive • Widely infiltrative • Rapid recurrence • Necrosis prone	• Gliobastoma multiforme (GBM) • Pineoblastoma • Medulloblastoma • Ependymoblastoma

2.5 Previous Studies:

Rahmad (2020) This is a cross-sectional analytic study involved 52 subjects that had proven brain tumor diagnosis during October 2017 - September 2018. Initially, 84 patients who had clinical symptoms of brain tumor and underwent management in Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital during October 2017-September 2018 were followed up. Among them, 63 patients who underwent conventional MRI, MRS, and histopathology examination were included. Eleven patients were then excluded due to negative results of a brain tumor after the complete examination. Informed consent was obtained from a total of 52 subjects who were admitted in this study. Conventional MRI was conducted with MRI Siemens 1.5 Tesla Avanto. MRI sequences included were T2WI (TR/TE 5160/112 ms, section thickness 5 mm; inter-section gap 1 mm; matrix 269 × 384 ; FOV 20.1 × 23.0 mm), T1WI (TR/TE 500/9.4 ms, section thickness 5 mm; inter-section gap 1 mm; matrix 256 × 256 ; FOV 23.0 × 23.0 mm), T1WI with contrast was done in all patients, T2 FLAIR (TR/TE 7000/92 ms; inversion time 2214.1 ms, section thickness 5 mm, inter-section gap 1 mm, matrix 230 × 256, FOV 23.0 × 23.0 mm). Multi voxel MRS was done with TR/TE 1690/135 ms, FOV 160.0 × 160.0 mm, VOI 80 × 80 mm (adjusted with the size of the tumor), slice thickness 25 mm, voxel 10 × 10 1 × 25, matrix 160 × 160 mm. The data used in this study was the score from Dean criteria, Choline/Creatine, Choline/NAA and the histopathological result of brain tumor biopsy as the gold standard. Conventional MRI using Dean criteria which include assessment of midline shift, edema, tumor signal heterogeneity, tumor hemorrhage, tumor margin, cyst/necrotic tumor tissue, and mass effect. Each of the points consist score from 0 to 2, and the range of the total score is 0-14. Choline/Creatine and Choline/NAA ratio derived from the calculated spectrum graph of MRS by comparing each of the respective metabolites of the lesion tissue and contra lateral normal tissue. Brain tumor defined as neoplasm in brain tissue originating from various type of tissue,

including tumor of brain tissue, cranial nerve tissue, meningeal tissue, and metastatic tissue. The grade of brain tumor was further classified into benign and malignant type of tumor using WHO Classification of Central Nervous System Tumor (2016) by histopathology examination. Grade I and II tumor were classified into the benign tumor while grade III and IV tumor were classified into malignant tumor group. Based on gender, the majority of the patients were female (78.8%, n=41). The mean age at diagnosis was 42.04 years old. According to age group, 69.2% of patients (n=36) belonged to 35-55 years of age group. Based on the Fisher-exact test and MannWhitney test, there were significant differences between the gender and age group compared to the type of brain tumor, respectively (p=0.007 and p=0.001). That meningioma (40.4%, n=41) contributes the majority of all the benign tumor and diffuse astrocytoma (3.8%, n=2) as the most common type of malignant tumors. Patients with Meningothelial meningioma (n=11, WHO grade I) had lower Dean scores, Choline/Creatine and Choline/NAA ratio compared to the patient with rhomboid meningioma (n=1, WHO grade III). There was no benign glioma patient admitted in this study. All of the glioma patients were malignant type glioma, which are diffuse astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, and oligoastrocytoma with Dean scores of 11±1.4, 7, 12, and 8, respectively. However, this study found that Choline/NAA yield a wide range of value from minimum 1,37 ppm to the maximum of 134.95 ppm for the malignant group and Choline/Creatine also has a maximum value of 25.63 ppm which is originated from a benign group. This was probably due to the data collection error. Despite these findings, there was a significant difference between the median of conventional MRI score and Choline/NAA ratio between benign and malignant brain tumor with $p<0.0001$ and $p=0.019$, respectively. MRS parameter to predict malignant brain tumor to conventional MRI score approached nearly 100%

Sankar (2018) Seventy histopathologically proved cases of gliomas were included in the study. Grade I and grade II gliomas were classified as low-grade and grade III and grade IV were classified as high-grade tumors. All patients underwent conventional MRI sequences and proton MR spectroscopy. Quantitative values were calculated for Cho/Cr, Cho/NAA, NAA/Cr, and lactate/Cr ratios. Grading by conventional MRI was also done to know the additional usefulness of MRS in grading of gliomas. The sensitivity, specificity, PPV, and NPV of conventional MRI in grading of gliomas were 62.2, 78.8, 76.7, and 65%, respectively, with the total diagnostic accuracy of 70%. The sensitivity, specificity, PPV, and NPV of proton MR spectroscopy in differentiating the grades of glioma were high in comparison to conventional MRI indicating that proton MRS spectroscopy is a useful tool in differentiating grades of glioma. Lac/Cr ratio had a total diagnostic accuracy of 95.12%. Cho/NAA and Cho/Cr ratios had a total diagnostic accuracy of 88.57 and 88.43%, respectively. Metabolite ratio that had the highest diagnostic value was lactate/Cr followed by Cho/NAA and Cho/Cr in differentiating low- and high-grade gliomas. NAA/Cr ratio had poor diagnostic significance in differentiating the grades of gliomas. The presence of lipid peak was found to be suggestive of high-grade gliomas and was found in about 46% of high-grade gliomas. Other metabolite peaks like myo-inositol and glutamate could not be evaluated. MRS had the added advantage in combination with conventional MRI with good diagnostic accuracy in differentiating grade II and grade III gliomas. Lactate/Cr had the highest diagnostic value followed by Cho/NAA and Cho/Cr in differentiating the two grades.

Yan Li (2017) The estimated line widths for Cho, Cr, and NAA in NAWM during 3T long TE MRSI were 6.4 ± 0.5, 5.4 ± 0.5, and 7.1 ± 0.5 Hz, respectively; for 3T short TE MRSI, they were 5.9 ± 0.3, 5.6 ± 0.3, and 8.5 ± 0.9 Hz, respectively, and for 7T short TE MRSI, they were 11.8 ± 1.1, 11.8 ± 1.8, and 15.5 ± 2.1 Hz, respectively (values expressed as means ± the standard

deviation). When expressed in terms of parts per million, these values corresponded to 0.043 ppm at 3T and 0.040 ppm at 7T for the Cr peak. The line widths of Cr in the T2 lesion were 5.5 ± 1.2, 6.0 ± 1.3, and 14.4 ± 3.4 Hz for the three acquisitions. These values are slightly higher than those previously reported for healthy volunteers. In conclusion, this study has evaluated metabolite profiles in patients with gliomas acquired with different TE and field strengths. Changes in T2 relaxation times caused differences in contrast for metabolite ratios between the three acquisition strategies. If the contrast between tumor and normal tissue is the primary consideration, conventional long TE MRSI at 3T gave the best and most reliable results for evaluating Cho and NAA. It is also the only method that when combined with spectral editing allows separate detection of lactate and lipid. As these are important for predicting the outcome in patients with high-grade glioma, long TE MRSI at 3T would be preferred as the most robust method for these subjects. For short TE acquisitions, there is a compromise between improved metabolite detection at 7T versus improved coverage and a reduced level of lipid contamination at 3T. This means that the lower field strength may be preferred for serial studies of large, heterogeneous tumors, while the higher field may be more relevant for smaller lesions.

Darweesh A N. et al(2014) studied Magnetic resonance spectroscopy and diffusion imaging in the evaluation of neoplastic brain lesions included thirty-six patients with histologically proven brain tumors (7 low, 13 high grade astrocytomas, 11 metastases, and 5 meningiomas) were evaluated with c MRI, MRS and DWI before surgery. They found that MR spectroscopy could differentiate benign from malignant tumors but was not useful in tumors grading. In the differentiation of malignant from benign tumors, N-acetyl aspartate (NAA), Choline (Cho), Creatine, lactate/lipid, and alanine ratios were significant. Increase in lipid and alanine could distinguish metastases and meningiomas from other tumors. Increase in the lactate level correlated with the

degree of malignancy. ADCs were effective for grading malignant tumors but not for distinguishing tumors types with the same grade. High grade malignant tumors had lower ADC values (0.428+0.006 · 10–3 mm2/s) than did low grade malignant (1.6+0.325 · 10–3 mm2/s), and benign (1.200+0.707 · 10–3 mm2/s) tumors. This study concluded that the combination of MRS with c MRI and calculated ADC values added more and more information to MR imaging in the differentiation and grading of brain tumors and were more useful when done together than each alone.

Julio, S., et al (2010) had studied how to Obtain a spectrum, that will analyzed, influenced by many factors, namely the physical and chemical characteristics of each metabolite and the compounds in which they are located; the selection of the area to study (cystic, solid, homogeneous, heterogeneous) together with the homogenization of the area (homogenization of the field and the sample, suppression of water signal), choice of the type of technique to be employed (mono voxel or multi voxel) and of the sequence to be used (PRESS, DRESS, SPARS, STEAM) and the choice of the echo time (short or long). Obtaining a spectrum adequate for analysis depends on the correct choice or application of all the above mentioned parameters, plus an appropriate cooperation on the part of the patient; this could give rise to differences observed by different researchers. In material and methods the various parameters used in obtaining the spectrum were mentioned.

However, it is worth pointing out that the spectra obtained at long TE were mainly analyzed due to:- the spectrum obtained is simpler to analyze, quantify and interpret, making the technique more reproducible in daily practice; at long echo times the resulting peak at 1.3 ppm is mainly composed of lactates because lipids have a short echo time and therefore, they would become saturated.

(Julio, Suarez, et al 2010)

John, R. H. et al (2010), had studied MRS that used to determine the degree of malignancy. As a general rule, as malignancy increases, NAA and Creatine decrease, and Choline, lactate, and lipids increase. NAA decreases as tumor growth displaces or destroys neurons. Very malignant tumors have high metabolic activity and deplete the energy stores, resulting in reduced Creatine. Very hyper cellular tumors with rapid growth elevate the Choline levels. Lipids are found in necrotic portions of tumors, and lactate appears when tumors outgrow their blood supply and start utilizing anaerobic glycolysis. To get an accurate assessment of the tumor chemistry, the spectroscopic voxel should be placed over an enhancing region of the tumor, avoiding areas of necrosis, hemorrhage, calcification, or cysts.

Multi-voxel spectroscopy is best to detect infiltration of malignant cells beyond the enhancing margins of tumors. Particularly in the case of cerebral glioma, elevated Choline levels are frequently detected in edematous regions of the brain outside the enhancing mass. Finally; MRS can direct the surgeon to the most metabolically active part of the tumor for biopsy to obtain accurate grading of the malignancy.

MRS cannot always distinguish primary and secondary tumors of the brain from one another. As mentioned above, one key feature of gliomas is elevated Choline beyond the margin of enhancement due to infiltration of tumor into the adjacent brain tissue. Most non-glial tumors have little or no NAA. Elevated alanine at 1.48 ppm is a signature of meningiomas. (***John, R. H., et al 2010***)

Alberto (2009) The objective of this work is to determine if the monovoxel MRS hydrogen proton (H+) long Eco Time (TE) is capable to differentiating or not the nature of the tumor from the brain lesions and classify them into levels of malignity. This is a retrospective study in which female and male patients of any ages were selected. A standard study of MRI was performed in them and it was completed with monovoxel ERM. The finding of this study that A total of 67 patients (36 women and 31 men) were gathered, but only the resulting

spectra of 57 patients were analyzed (47 of which presented lesions and 10 belonged to the normal control group), 33 women (57.9%) and 24 men (42.1%), aged between 12 and 81 years (35 years average). Ten patients (3 women and 7 men) were excluded, one of them had a brain tumor and we lacked the pathology results for comparison; and as for the remaining 9, a spectrum with too much artifact and poor quality was obtained, not allowing for a proper analysis. 43 of 47 brain lesions (92.9%) were properly characterized, with 3 false-positive findings and 1 false-negative, yielding the following statistical values: S of 96.8% (CI 89-100), E of 89, 6 (IC 76-100), PPV of 91.1% (CI 80-100) and a NPV of 96.3% (CI 87-100) (Graphic 1). NTL group was composed of a total of 18 patients: 8 in the subgroup of lesions with gliosis, 4 in the cystic-necrotic lesions and 6 in the inflammatory demyelinating lesions (most did not undergo biopsy but just progressive control because its appearance and evolution were benign and showed no change except a necrotic lesion and a progressive multifocal leuko encephalopathy (PML), which were false-positive findings). In the LGT group, 15 patients were included (Ganglioglioma (n=1); TNED (n=1), Hematoma (false positive) (n=1), grade I Astrocytoma (WHO) (n=2); Grade II Astrocytoma (n=5), Oligodendroglioma (n=4) and Oligoastrocytoma (n=1)). The AT group was composed of 6 patients (Anaplastic Astrocytomas (n=3) and Anaplastic Oligodendroglioma (n=3)). GBM-MTS group was consisted of 8 patients (GBM (n=5) and MTS (n=3), melanoma (false negative), lung and breast). Lastly the normal control group was composed of 10 patients (Tables and Graphics 2 to 9). In the gliosis cases a mild increase in Cho was identified together with a decrease of NAA, and a slight increase in Lac was observed in one case. In necrosis or cystic lesions, a marked decrease of all peaks was measured with a significant increase of Lip and Lac . In the group of demyelinating or inflammatory lesions, in most cases, a slight increase in the Cho peak was observed while the NAA peak remained slightly decreased and, in about half of the cases, a slight increase Lip and Lac

was shown. In the group of LGT, it was found that most lesions had an increase of Cho and a decrease of NAA in relation to neo proliferation and cell injury respectively; significant Lip and Lac peaks were not identified. In contrast, in the AT a significant increase of Cho was noticed as well as a significant decrease of NAA; elevated peaks in the spectrum for Lip and Lac were also observed Finally, in the GBM-MTS group a significant increase in Cho was not always found, probably due to a larger component of necrosis, though it did show a marked decrease of NAA and a significant increase of the peaks in the area of Lip and Lac The study conclude MRS together with the MRI proved to be a reliable method to determine whether a brain lesion is a tumor or not, with acceptable statistic values.

Kumar, A. K. S., et al (2011), had studied Proton MRS to improve the diagnostic accuracy preoperatively in brain tumors, even obviating stereotactic biopsies in some cases (especially the inoperable tumors), and helping in monitoring the response to therapeutic surgical/medical intervention. The metabolites routinely assessed include Cho, Cr, NAA, Lac and Lipids. Cho from choline-based compounds (acetylcholine,

phosphocholine, glycero-phosphocholine), involved in cell membrane bio-synthesis and turnover, is elevated in processes involving increased membrane formation and cell proliferation. Cr from phosphocreatine and creatine is involved in energy metabolism. As Cr resonance intensity is relatively invariant and uniform throughout the normal brain tissue, it is used as an internal standard against which resonance intensities of other metabolites are normalized. However, Cr may be reduced in hyper metabolic and raised in hypo metabolic states. NAA, a neuronal marker, is decreased in processes involving neuronal loss or damage. Lac and lipid peaks are not observed in a normal brain spectrum. Presence of lactate, an end-product of anaerobic glycolysis, is an indirect index of ischemic and hypoxic conditions. A lipid signal may be detected in conditions leading to disruption of cell membranes and myelin

sheaths. The typical 1H-MRS characteristics of gliomas include elevated Cho signal with reductions in NAA and Cr peaks; along with lactate/lipid peaks in some cases. Elevation of Cho in mitotic lesions reflects increased membrane synthesis and cellularity. Elevated Cho/Cr ratio is generally correlated with an increase in tumor malignancy and used as a possible non-invasive index of tumor grading. ***(Kumar, A., K., S. ,et al 2011)***

Harish, P., R.,G., R., K, et al (2012), had studied NAA as a neuronal marker and decreases in all tumors because of the invasiveness of tumor cells within the normal tissue.

Proton MR spectroscopy–visible Cho-containing compounds include acetyl choline, glycerophosphate membrane turnover and cell proliferation.

Cr/phosphocreatine, an indicator of energy phosphocholine, and phosphocholine. Cho is increased in all tumors because of increased metabolism, shows variable signal intensity in proton MR spectroscopy of intracranial tumors.

Gliomas have been graded on the basis of NAA/Cho, Cho/Cr, NAA/Cr, and lactate/Cr ratios. NAA/ Cho and Cho/Cr ratios have shown consistency in predicting the tumor grade, we observed NAA peak in only 12 of 37 cases of high-grade gliomas.

The comparison of NAA/ Cho and Cho/Cr ratios in these cases with that of the low-grade gliomas provided a significant difference between the two groups. In the present study, NAA/Cr ratio did not provide any significant correlation with the degree of malignancy.

Most tumor cells have low respiration and high glycolysis rates even when oxygen levels are sufficient for respiration. The high glycolytic rate results in increased accumulation of pyruvate, which converts to lactate, because there is a decrease in the tri carboxylic acid cycle activity in brain tumors. Alternatively, lactate also may be produced by anaerobic glycolysis in tumors with hypoxia. Increased low-grade gliomas. Lactate in all the low grade gliomas and most

high-grade gliomas in the present study suggest that its presence does not correlate with the grade of malignancy. Lipid resonances have been observed in high-grade gliomas on in vivo studies using different echo times, in areas of MR imaging especially. The presence of NAA in metastases, on in vitro and in vivo studies, is attributed to the presence of normal brain parenchyma in infiltrating lesions or the partial volume effects with adjacent brain tissue. The presence of a small broad resonance at 2.02 ppm, in five cases, along with resonances at 1.3 ppm and 0.9 ppm is probably attributable to the methylene.

(***Harish, P., R.,G., R., K, et al. 2012***)

Delorme (2006) Magnetic resonance spectroscopy (MRS) has clinically been most extensively used for assessing brain disorders, particularly tumors. With 1-H spectroscopy at intermediate echo times, resonances from choline, creatine, N acetyl-aspartate (NAA), lactate, and free fatty acids can be resolved well enough to assist in diagnosis under routine conditions. Generally, an increased concentration of choline is found in all primary and secondary brain tumors, and the degree of increase correlates with the degree of anaplasia. Further indicators of anaplasia are the presence of lactate, indicating hypoxia, and of fatty acids, indicating necrosis. According to literature, the sensitivity of a combination of proton spectroscopy with contrast-enhanced dynamic susceptibility-weighted imaging for high-grade components in gliomas is better than conventional contrast-enhanced imaging alone. Today, proton spectroscopy is clearly indicated for differentiating radiation-induced damage from recurrences of irradiated brain tumors. A normal spectrum with a low choline and high NAA peak makes a tumor highly improbable, and rather suggests a scar, heterotopia, or other benign condition. In patients with a known extra cranial primary and an appropriate risk constellation, a contrast-enhancing brain lesion may be confidently diagnosed as a metastasis. In some instances, however, the diagnosis is not very clear, e.g. when no primary tumor is known (or a primary tumor is unlikely to cause brain metastases), or with solitary lesions which are

rather irregular but round. Metastases should not contain NAA (if they do, this is mostly due to partial volume effects). High-grade gliomas, which may be morphologically indistinguishable from metastases, usually show some level of NAA, although low. Gliomas and metastases have in common an elevation in choline, a low concentration of creatine, and the presence of lipids and/or lactate . Notably, whenever both lipids and lactate are present this cannot be further differentiated since they share a resonance frequency. Usually the lipid peak will predominate. In some instances, with high-grade gliomas, no NAA will be detected due to necrosis, making the discrimination from a metastasis difficult. Here, it may be helpful to assess the T2-hyperintense, non-enhancing rim. In the presence of a high-grade glioma this rim is usually diffusely infiltrated by low-grade components and will therefore show a depression of NAA and increase in the choline resonance . With metastases, however, this rim is usually simple vasogenic edema, and the spectrum will be that of normal brain. Primary lymphoma of the brain may be morphologically difficult to discriminate from high-grade glioma. As with metastases, the absence of NAA may assist the differential diagnosis. The diffusely infiltrating character in turn will help to distinguish between lymphoma and metastasis.

Stadlbauer, et al(2006), had studied a technique that detects metabolites, such as n-acetyl aspartate, Choline-containing compounds, Creatine/phosphocreatine, and lactate Measurements of metabolite ratios provide diagnostic information that adds to that obtained by MRI alone. MRS can be valuable in the diagnosis of leukodystrophies and mitochondrial disorders. Providing prognostic information in neonatal hypoxia/ischemia. Differentiating among brain tumors, staging, and identifying a suitable biopsy site Differentiating between tumor progression and radiation necrosis. In most cases, single voxel MRS is used to obtain chemical information from a region of interest measuring 2x2x2 cm; in multi voxel MR spectroscopic imaging (MSRI), the voxel size is 1 cm3. ***(Stadlbauer, et al 2006)***

Harish (199%) This study wanted to assess the use of in vivo proton MR spectroscopy for characterization of intracranial mass lesions and to ascertain its reliability in grading of gliomas.. One hundred twenty patients with intracranial masses were subjected to volume selective spectroscopy using stimulated echo acquisition mode (echo time, 20 and 270 milliseconds) and spin echo (echo time, 135 milliseconds) sequences. The intracranial lesions were grouped into intra axial and extra axial, as judged with MR imaging. Assignment of resonances was confirmed in two samples each of brain abscess, epidermoid cyst, and tuberculoma using ex vivo high-resolution MR spectroscopy. RESULTS**:** The in vivo spectra appeared distinct compared with normal brain in all the cases. All high-grade gliomas (n 5 37) showed high choline and low or absent *N*-acetyl-L-aspartate and creatine along with lipid and/or lactate, whereas low-grade gliomas (n 5 23) were characterized by low *N*-acetyl aspartate and creatine and high choline and presence of only lactate. *N*-acetyl aspartate/choline ratio was significantly lower and choline/creatine ratio was significantly higher in high-grade gliomas than in low-grade gliomas. Presence of lipids suggested a higher grade of malignancy. All metastases (n 5 7) showed lipid and lactate, whereas choline was visible in only four cases. Epidermoid showed resonances from lactate and an unassigned resonance at 1.8 ppm. Meningiomas could be differentiated from schwannomas by the presence of alanine in the former. Among the infective masses, pyogenic abscesses (n 5 6) showed resonances only from cytosolic amino acids, lactate, alanine, and acetate; and tuberculomas (n 5 11) showed only lipid resonances. CONCLUSIONS**:** In vivo proton MR spectroscopy, helps in tissue characterization of intracranial mass lesions. Spectroscopy is a reliable technique for grading of gliomas when *N*-acetyl-aspartate/choline and choline/creatine ratios and presence of lipids are used combination.

Grand, et al. (1999 **)** had studied how the advanced MRI techniques provide useful, complementary information for grading gliomas, in comparison with

conventional MRI. Echo planar diffusion, perfusion MRI and multi voxel proton MRS can offer diagnostic conventional MRI, in the assessment information, not available with of glioma grade. Gliomas, the most frequent primary brain tumors, are histologically heterogeneous, representing a biologic continuum with varying degrees of cellular and nuclear pleomorphism, mitotic activity, vascular proliferation and necrosis. Although conventional MRI with gadolinium-containing contrast media has been useful for characterizing brain tumors. Although single-voxel MRS has been reported to be useful for investigation of gliomas, it is difficult to assess the spatial distribution of spectral changes.

Recent developments in MRS have made it possible to obtain chemical-shift imaging (CSI) with high spatial resolution and multiple spectra simultaneously from contiguous voxels. ***(Grand, et al 1999***)

Chapter Three

Materials and methods

chapter There

Materials and methods

3.1 Materials:

This study was done at Sudan University of Science and Technology, College of Graduated Studies & Scientific Research and Royal car international hospital, Almoalem medical city hospital, Khartoum Sudan during the period from SEP 2017—MAR 2020.

During a period of 24 months the data will be collected from 200 patients (male & female at any age) from diagnostic department record system MRI PACS of Royal care international hospital and Almoalem medical city hospital, Khartoum- Sudan, which is doing MRI & MRS for investigation of brain lesions.

The data will be collected using standard data sheet including patient age, gender, clinical history, location of the tumors and MRI & MRS finding.

3.2 Machine:

The study will carried out in Royal care hospital using Toshiba Excelart Vantage

1.5 Tesla MRI machine and Almoalem medical city using semines MRI machine 1.5 Tesla.

3.3 Study duration:

This study will take a period of about 24 months to give full evaluation of brain lesions by using MRS.

3.4 Study population:

The cases of this study consisted of **200** patients (male & female) in different ages, gender, , condition and location of the lesions. All of those patient's have been investigated by MRI & MRS and the result is brain lesions which reported by experienced radiologist.Most of patients will included in my studies were diagnosed with brain lesion by MRI and advised to do MRS which is confirm the presence of brain Tumor and nonneoplastic lesion.

3.5 Data Collection:

The data will be collected from the record system of MRI department (PACS)of Almoalem medical city hospital and Royal care international hospital (Khartoum - Sudan). The equipment used in Royal care hospital is Toshiba Excelart Vantage 1.5 Tesla MRI machine. Almoalem medical city used semines MRI machine 1.5 Tesla .

3.6 Techniques:

In both hospitals do MRI brain for the patients by lies The patient supine on the examination couch with their head within the head coil, the head is adjusted so that the inter papillary line is parallel to the couch and the head is straight. The patient is positioned so that the longitudinal alignment light lies in the midline, and the horizontal alignment light passes through the nasion Straps and foam pad are use for immobilization and then enter to the gantry of MR and then applied the MR protocols (T_1, T_2, diffusion and flair). T_1 weighted image after intravenous gadolinium administration were obtained at least 2 planes After MRI image done.MRS will added to provides information about the relative concentration of certain chemical compounds with selected volume of tissue , MRS requires a standard radiofrequency (RF) coil and dedicated software package like (PRESS) technique(imaging flip angle 90-180,TE 136,TR (1500-2000),SNR 100%,matrix 64,FOV 22,no warp 1.0,slice thick 2.00, time 4.16,48).All spectroscopy images in my study were performed through single-voxel technique (SVS). Initially localization methods used to localized the voxel from MR image in a clinical proton MR spectroscopy, point – resolved surface coil spectroscopy (PRESS) the voxel size is 2×2×2 cm3 (8 ml), , then voxel was placed on volume of interest and suppression of water signal done by use chemical shift selective expiation (CHESS) . while suppression of fat done by avoid the area of lesion contain fat. Analysis of the differences in metabolite resonance frequency can only be performed in the presence of highly homogenous magnetic field. A heterogeneous magnetic field leads to resonance

frequency dispersion. Spreading out the peaks or even causing them to disappear into the background noise. Prior to any MRS acquisition, the magnetic field is homogenized (shimming) in the region of interest. The bigger region the harder it's to homogenize the zones magnetic field throughout. Close to the bone, calcifications or hemorrhagic, MR spectroscopic studies are obtained using a localized single volume (PRESS) however, using chemical – shift imaging it is possible to obtain one or two-dimensional data sets that display metabolites from adjacent compartments encompassing a large tissue volume and to give imaging as mapping explaining the concentration of metabolites in MRS image. MR spectroscopy are capable of echo times (TEs) as short as 20 milliseconds adequate allow for identify the signal from most metabolites have short time of echo and obtained TEs as long as 136 milliseconds and TR 2000 ms to allow for identify the signal from metabolites in the brain have long TE. Multiple MR spectra obtained, some in lesion area and one in the normal brain during 10 to 15 minute .After doing the investigation of MRI & MRS brain the image send to (PACS) system and the result reporting from the radiologist send also, I will take the data from the PACS without name by the number of patient give to here from the reception department .data will be collected through collection data sheet adopted for the study during a period of 24mouths the data has been collected from 200patients{male &female at any age }from diagnostic department record system MRI PACS(group A) of Almoalem medical city hospital and (group B) of Royal care international hospital (Khartoum- Sudan), which is doing MRI & MRS for investigation of brain lesion. The data has been collected using standard data sheet including patient age, gender, location of the tumors, level of , Ch/Cr, NAA/Cr ratio, NAA, Lip/lac and MRI & MRS finding.

3.7 Data collection sheet:

No	Age	Sex	Location of lesion	MRI finding	**Cho/Cr ratio**	**NAA/Cr ratio**	**NAA**	**Lipid/Lac**	**MRS finding**

3.8 Data analysis:

Data will be analyzed by using the computerized program, statistical methods (**SPSS**)statistical package for social science. for group (**A**) The data were analyzed using SPSS version 19. Frequency and percentage are estimated for categorical variables using descriptive statistics. The independent student t-test and one -way Anova tests were performed to compare the neoplastic and non neoplastic masses and assess the mean ratios among different brain lesion, p value is significant 0.001 or 0.05. group (**B**) after the data collected it was analyses using SPSS version 23. Frequency and percentage are estimated for categorical variables. The Chi square tests were done to assess the relationship of metabolites results and type of lesion suggestive on MRS, p value significant if less than 0.01 or 0.05 respectively.

3.9Study variables:

The findings were compared the MRI findings and MRS findings.

3.10 Ethical consideration:

APPROVAL for this study will be obtained from Sudan University of science and technology –medical radiological science, college of post graduated studies Khartoum state ministry of health research department.

3.11 Informed consent

Written consent was obtained from Royal care international hospital(ethical approval code: MH/KS/PMI/44/A/2). and Almoalem medical city. The data collected from PACS in radiology department. There is no patient identification or individual patient detail will be published.Also **confidentiality** will be ensured by making the collected data accessible only to the researcher. And also I will keep all data collected during the study on computer protected by pass ward. All paper format data will be stored in locked cabinet.This data will be used only for scientific research purposes.

Chapter four

Results

Chapter four

Results

Regarding the spectroscopy findings, all the patients had a previous conventional MRI image which was not conclusive. The participating patients in this study was 200 patients who attended radiology department in Almoalem medical city and Royal care international hospital ,investigated by MRS for evaluation of brain lesions which distribute the participants into two groups(**A**&**B**) , so the detailed results are shown in the tables and figures below.

Results group A

Table (4.1) shows gender distribution:

Gender	Frequency	Percent	Valid Percent	Cumulative Percent
Male	54	54.0	54.0	54.0
Female	46	46.0	46.0	100.0
Total	100	100.0	100.0	

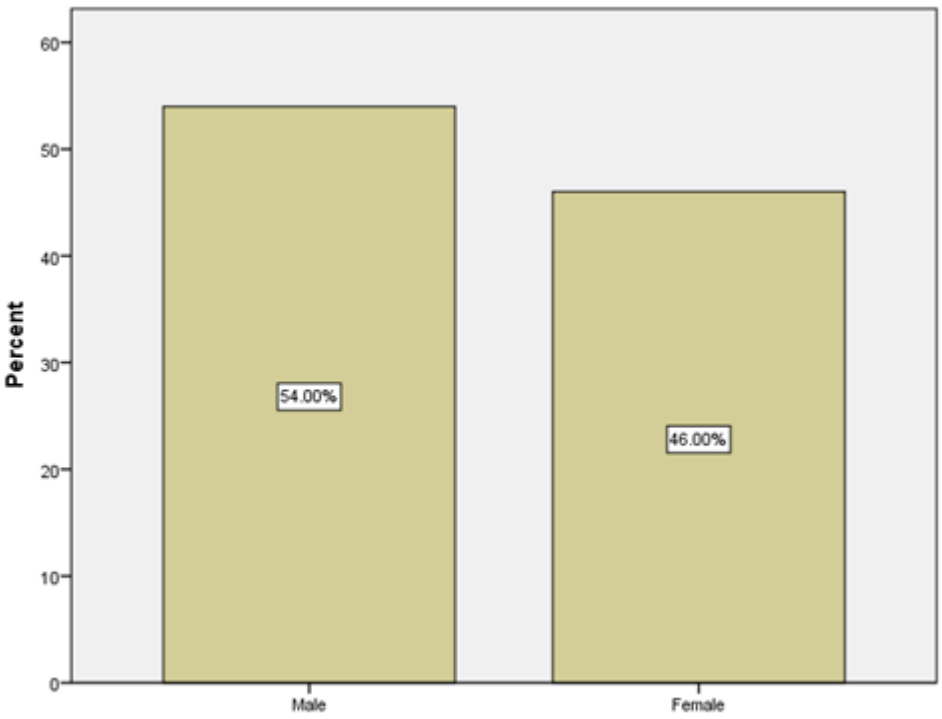

Figure (4.1) frequency distribution of gender

Table (4.2) frequency distribution of age:

Age	Frequency	Percent	Valid Percent	Cumulative Percent
1-17	10	10.0	10.0	10.0
18-28	21	21.0	21.0	31.0
29-39	8	8.0	8.0	39.0
40-50	17	17.0	17.0	56.0
51-61	26	26.0	26.0	82.0
62-72	13	13.0	13.0	95.0
73-83	4	4.0	4.0	99.0
84-90	1	1.0	1.0	100.0
Total	100	100.0	100.0	

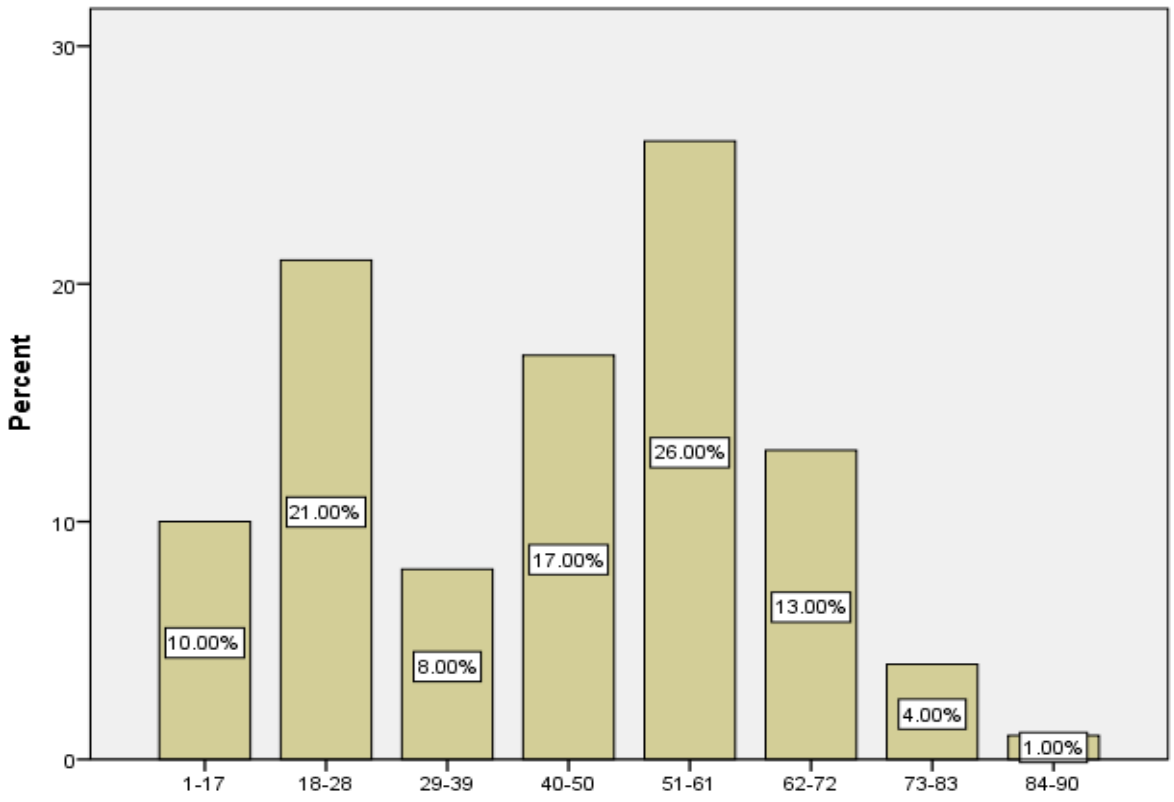

Figure (4.2) frequency distribution of age

Table (4.3) Descriptive statistic for age, Cho/Cr and NAA/Cr ratios:

Variables	N	Minimum	Maximum	Mean	Std. Deviation
Age	100	1	90	43.75	20.083
NAA/Cr ratio	100	0.08	7.87	1.8123	1.30016
Cho/Cr ratio	100	0.65	10.98	3.8204	1.89440
Valid N (list wise)	100				

Table (4 .4) Cho/Cr and NAA/Cr ratios in different brain lesions(P-value >0.05):

Final MRS diagnosis	**Cho/Cr**	**NAA/Cr**
	Mean± SD	
GBM	4.37±1.66	1.45±0.67
Glioma	3.88±2.22	2.28±1.66
Mets	3.55±1.23	1.92± 0.65
Astrocytoma	3.36±2.35	1.80 ±0.73
Neoplastic process	4.16±2.09	1.67 ±1.21
Lymphoma	4.25±1.68	0.61± 0.39
Abscess	1.71± 0.73	1.85± 1.28
Meningiomas	3.87±2.11	2.53 ±2.59
Inflammation	1.00±0.00	1.40±0.00
Tuberculoma	2.51±1.16	1.20± 0.48
Granuloma	2.22±.183	1.83± 0.07
DENS	3.62±0.00	2.55±0.00
Radiation necrosis	1.03±0.00	2.04±0.00

Table (4.5)Comparison between neoplastic and nonneoplastic brain lesions in Cho/Cr and NAA/Cr ratios (independent sample t-test):

Metabolites ratios	**Neoplastic**	**Nonneoplastic**	**P value**
Cho/Cr (Mean ±SD)	3.95±1.87	1.74±.67	<0.001**
NAA/Cr (Mean ±SD)	1.80±1.32	1.79 ±1.18	>0.5

Table (4.6) frequency distribution of NAA:

NAA	Frequency	Percent	Valid Percent	Cumulative Percent
Reduced	93	93.0	93.0	93.0
Absent	7	7.0	7.0	100.0
Total	100	100.0	100.0	

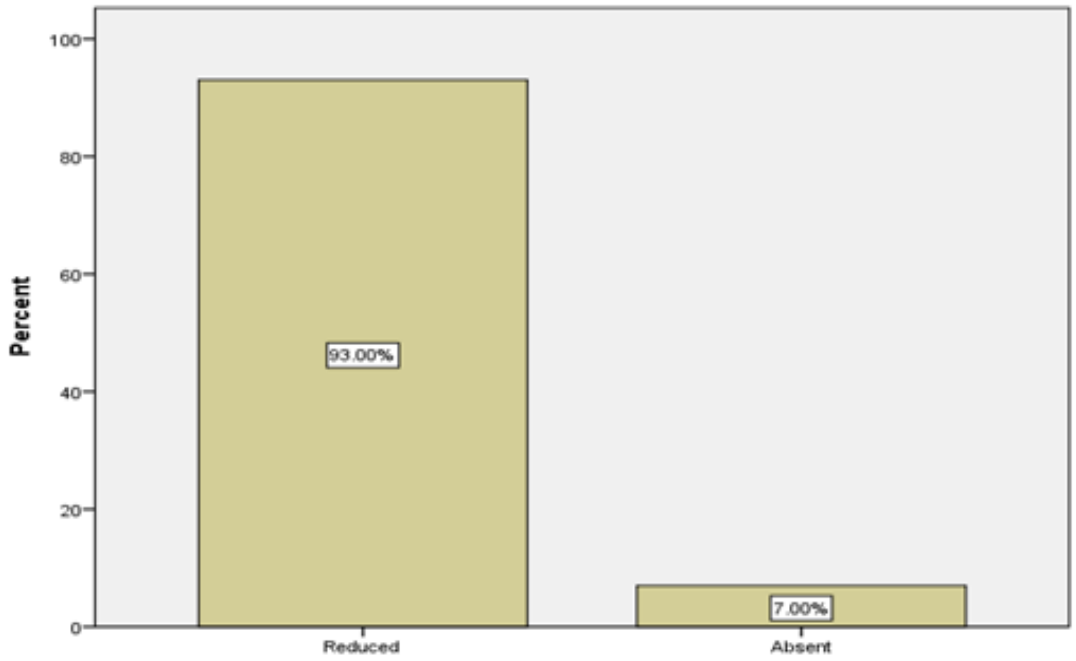

Figure (4.3) frequency distribution of NAA

Table (4.7) frequency distribution of lipid –lactate:

Lipid-lactate	Frequency	Percent	Valid Percent	Cumulative Percent
Moderate elevation	45	45.0	45.0	45.0
Mild elevation	31	31.0	31.0	76.0
Normal	21	21.0	21.0	97.0
Normal +Alanine	3	3.0	3.0	100.0
Total	100	100.0	100.0	

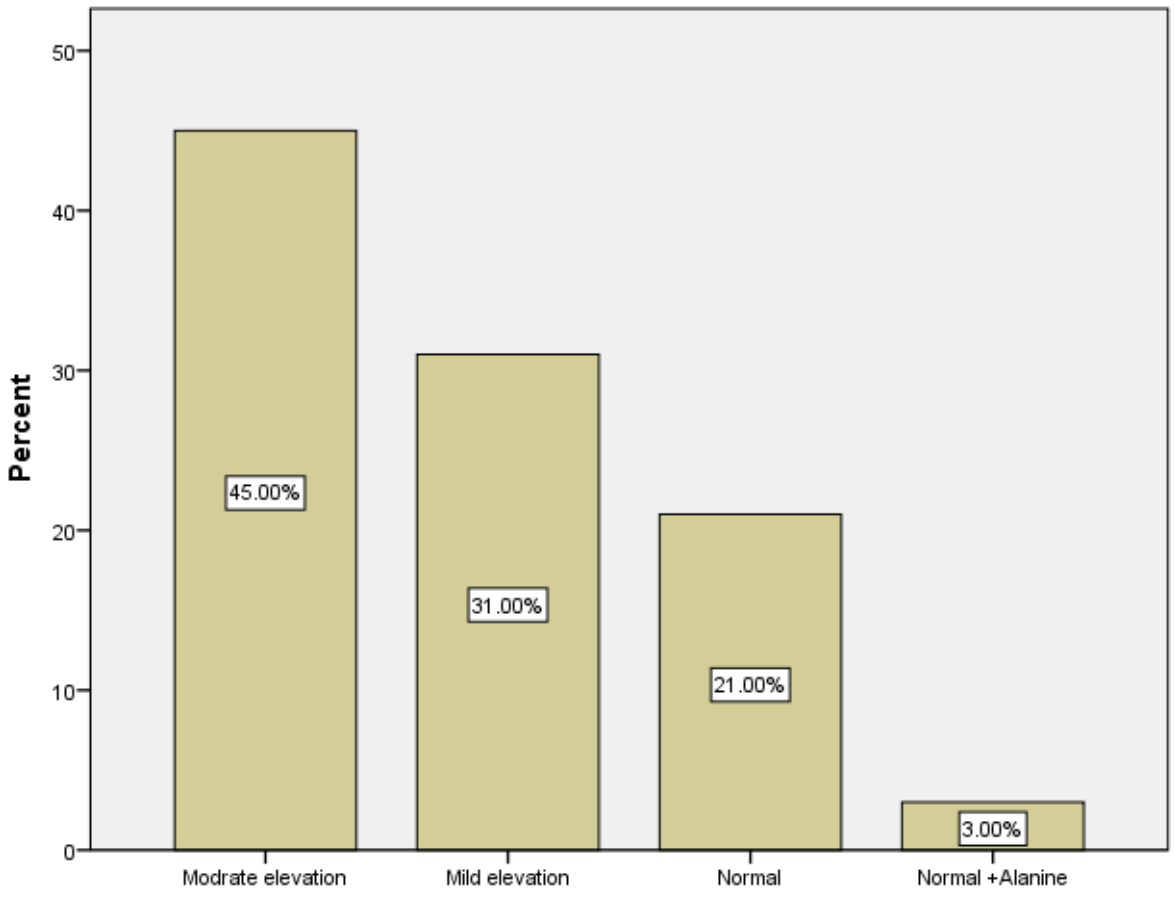

Figure (4.4) frequency distribution of lipid -lactate

Table (4.8) frequency distribution of MRI findings:

MRI FINDINGS	Frequency	Percent	Valid Percent	Cumulative Percent
Abscess	1	1.0	1.0	1.0
Abscess ? Glioma	2	2.0	2.0	3.0
Abscess or GBM	1	1.0	1.0	4.0
Abcess?metastasis	1	1.0	1.0	5.0
Bi frontal lesion	1	1.0	1.0	6.0
Brain mass? Metastasis	1	1.0	1.0	7.0
Brain stem lesion	1	1.0	1.0	8.0
Brain tumor	2	2.0	2.0	10.0
Brain tumor / lymphoma	1	1.0	1.0	11.0
Cerebellar Glioma	1	1.0	1.0	12.0
corpus callosum lesion	1	1.0	1.0	13.0
Cystic lesion ? Low grade glioma	1	1.0	1.0	14.0
Enhancing mass lesion	1	1.0	1.0	15.0
Extra axial enhancing lesion	1	1.0	1.0	16.0
Extra axial mass	1	1.0	1.0	17.0
Focal cerebral lesion	1	1.0	1.0	18.0
Frontal lesion	2	2.0	2.0	20.0
GBM	3	3.0	3.0	23.0
Glioma	1	1.0	1.0	24.0
Glioma ? Abscess	1	1.0	1.0	25.0
Gliosis ? Metastasis	1	1.0	1.0	26.0
Granuloma	1	1.0	1.0	27.0
Heterogeneously enhancing lesion	1	1.0	1.0	28.0
Hippocampus lesion	1	1.0	1.0	29.0
Hypothalamic enhancing mass	1	1.0	1.0	30.0
Infection/neoplasm	1	1.0	1.0	31.0
Intra-axial lesion	2	2.0	2.0	33.0
Intra-pranchymal lesion	1	1.0	1.0	34.0
Intravascular lesion	1	1.0	1.0	35.0
Intraventircular enhancing lesion	1	1.0	1.0	36.0
Large butterfly lesion	1	1.0	1.0	37.0
Lesion	3	3.0	3.0	40.0

Table (4.8) Count:

MRI FINDINGS	Frequency	Percent	Valid Percent	Cumulative Percent
LF parietal lesion	1	1.0	1.0	41.0
LF posterior parasigttal lesion	1	1.0	1.0	42.0
Low grade glioma	3	3.0	3.0	45.0
LT cortically based frontal lesion	1	1.0	1.0	46.0
LT frontal lesion	1	1.0	1.0	47.0
LT frontal mass	1	1.0	1.0	48.0
LT parietal lesion	2	2.0	2.0	50.0
LT parasegettal mass	1	1.0	1.0	51.0
LT parasigittal mass	1	1.0	1.0	52.0
LT posterior frontal ring enhancing lesion	1	1.0	1.0	53.0
LT ring enhancing lesion	1	1.0	1.0	54.0
LT temporal lesion	1	1.0	1.0	55.0
Mass ? Infection	1	1.0	1.0	56.0
Mass ? Metastasis	1	1.0	1.0	57.0
Meningioma	1	1.0	1.0	58.0
Metastasis	5	5.0	5.0	63.0
Multiple enhancing brain lesion	1	1.0	1.0	64.0
Multiple infra &supra enhancing lesion	1	1.0	1.0	65.0
Multiple intra axial enhancing lesion	1	1.0	1.0	66.0
Multiple LT tempro-paraito occipital lesion	1	1.0	1.0	67.0
Neoplastic process	1	1.0	1.0	68.0
Parasellar mass	1	1.0	1.0	69.0
Parietal lesion	1	1.0	1.0	70.0
Petro-Celival mass	1	1.0	1.0	71.0
Pontine lesion	3	3.0	3.0	74.0
Posterior fossa tumor	1	1.0	1.0	75.0
Ring enhancing lesion	7	7.0	7.0	82.0

Table (4.8) Count:

MRI FINDINGS	Frequency	Percent	Valid Percent	Cumulative Percent
RT basal ganglia lesion	1	1.0	1.0	83.0
RT frontal lesion	1	1.0	1.0	84.0
RT hypocampal tumor? glioma	1	1.0	1.0	85.0
RT hypothalamus enhancing lesion	1	1.0	1.0	86.0
RT occipital lope mass	1	1.0	1.0	87.0
RT parasigtal mass	1	1.0	1.0	88.0
RT parietal lesion	2	2.0	2.0	90.0
RT parietal mass	1	1.0	1.0	91.0
RT side lesion	1	1.0	1.0	92.0
S.O.L	1	1.0	1.0	93.0
S.O.L ?metastasis ?tuberculoma	1	1.0	1.0	94.0
S.O.L /tuberculoma	1	1.0	1.0	95.0
Tembro-paraital lesion	1	1.0	1.0	96.0
Temporal lesion	1	1.0	1.0	97.0
Tuberculosis	1	1.0	1.0	98.0
Vascular malformation	1	1.0	1.0	99.0
Ventricular abscess	1	1.0	1.0	100.0
Total	100	100.0	100.0	

Table (4.9) frequency distribution of MRS finding:

MRS Finding	Frequency	Percent	Valid Percent	Cumulative Percent
GBM	24	24.0	24.0	24.0
Low grade glioma	14	14.0	14.0	38.0
Neoplastic process	11	11.0	11.0	49.0
Metastasis	7	7.0	7.0	56.0
Meningioma	6	6.0	6.0	62.0
Abscess	5	5.0	5.0	67.0
Glioma	5	5.0	5.0	72.0
Lymphoma	3	3.0	3.0	75.0
Tuberculoma	3	3.0	3.0	78.0
High grade glioma	2	2.0	2.0	80.0
Polycystic astrocytoma	2	2.0	2.0	82.0
Aggressive brain tumor	1	1.0	1.0	83.0
Aggressive neoplasm	1	1.0	1.0	84.0
Aggressive intra ventricular tumor	1	1.0	1.0	85.0
DENT	1	1.0	1.0	86.0
Granuloma	1	1.0	1.0	87.0
Hemorrhagic neoplasm	1	1.0	1.0	88.0
High grade neoplasm	1	1.0	1.0	89.0
Inflammatory	1	1.0	1.0	90.0
Intracranial metastasis	1	1.0	1.0	91.0
Lymphoma/Glioma	1	1.0	1.0	92.0
Malignant cerebellar + metastasis	1	1.0	1.0	93.0
Malignant meningioma	1	1.0	1.0	94.0
Neoplastic process/Clivel chordoma	1	1.0	1.0	95.0
Primary brain tumor	1	1.0	1.0	96.0
Radiation necrosis \PNET	1	1.0	1.0	97.0
Tuberculosis granuloma	1	1.0	1.0	98.0
Tuberculosis glioma	1	1.0	1.0	99.0
Ventriculitis/abscess	1	1.0	1.0	100.0
Total	100	100.0	100.0	

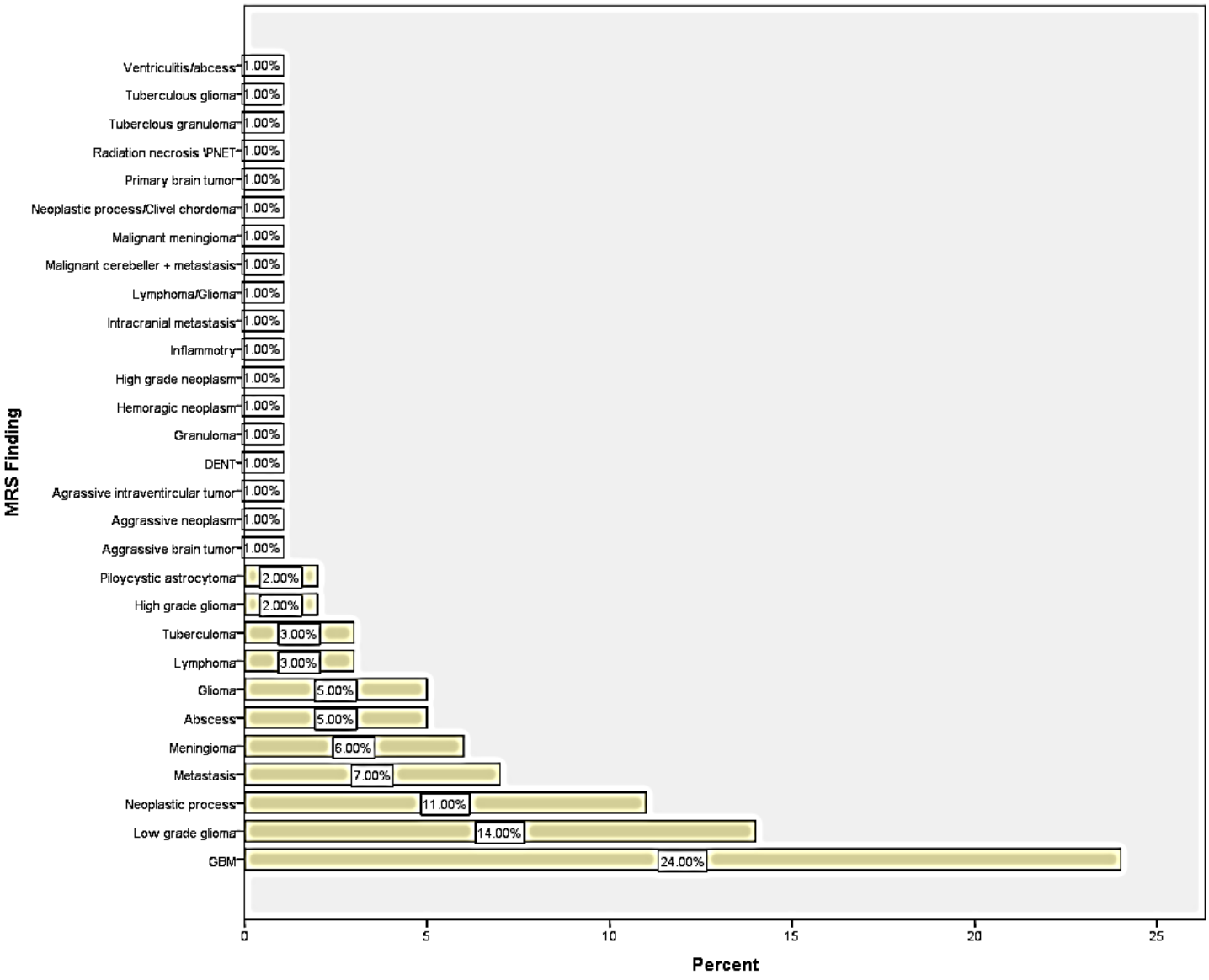

Figure (4.5) frequency distribution of MRS finding

Table (4.10) cross tabulation MRS finding and NAA:

MRS finding	NAA		Total
	Absent	Reduced	
GBM	1	23	24
Low grade glioma	0	14	14
Neoplastic process	0	11	11
Metastasis	0	6	7
DENT	1	1	1
Abscess	0	5	5
Glioma	0	5	5
Granuloma	0	1	1
Hemorrhagic neoplasm	0	1	1
High grade glioma	0	2	2
High grade neoplasm	0	1	1
Inflammatory	1	0	1
Intracranial metastasis	0	1	1
Aggressive brain tumor	0	1	1
Lymphoma	0	3	3
Lymphoma/Glioma	0	1	1
Malignant cerebellar + metastasis	0	1	1
Malignant meningioma	1	0	1
Meningioma	3	3	6
Aggressive intra ventricular tumor	0	1	1
Aggressive neoplasm	0	1	1
Neoplastic process/Clivel chordoma	0	1	1
Polycystic astrocytoma	0	2	2
Primary brain tumor	0	1	1
Radiation necrosis \PNET	0	1	1
Tuberculosis granuloma	0	1	1
Tuberculoma	0	3	3
Tuberculosis glioma	0	1	1
Ventriculitis/abscess	0	1	1
Total	7	93	100
P value =0.011			

Table (4.11) cross tabulation MRS finding and lipid –lactate:

MRS finding	LIPD/ LACTATE				Total
	Mild elevation	Moderate elevation	Normal	Normal +Alanine	
Abscess	0	5	0	0	5
Aggressive brain tumor	1	0	0	0	1
Aggressive neoplasm	0	1	0	0	1
Aggressive intra ventricular tumor	0	1	0	0	1
DENT	1	0	0	0	1
GBM	7	17	0	0	24
Glioma	2	1	2	0	5
Granuloma	0	1	0	0	1
Hemorrhagic neoplasm	0	0	1	0	1
High grade glioma	0	2	0	0	2
High grade neoplasm	1	0	0	0	1
Inflammatory	0	0	1	0	1
Intracranial metastasis	0	1	0	0	1
Low grade glioma	7	0	7	0	14
Lymphoma	1	1	1	0	3
Lymphoma/Glioma	0	1	0	0	1
Malignant cerebellar + metastasis	0	1	0	0	1
Malignant meningioma	0	0	1	0	1
Meningioma	0	0	3	3	6
Metastasis	3	2	2	0	7
Neoplastic process	6	4	1	0	11
Neoplastic process/Clivel chordoma	0	0	1	0	1
Polycystic astrocytoma	1	1	0	0	2
Primary brain tumor	0	0	1	0	1
Radiation necrosis\PNET	0	1	0	0	1
Tuberculosis granuloma	0	1	0	0	1
Tuberculoma	0	3	0	0	3
Tuberculosis glioma	0	1	0	0	1
Ventriculitis/abscess	1	0	0	0	1
Total	31	45	21	3	100
P value =0.001					

Table 4.12 Compare means CHO-CR and NAA-CR ratio with MRS finding

MRS Finding		Cho/Cr ratio	NAA/Cr ratio
Abscess	Mean	1.8560	2.1500
	Std. Deviation	0.72628	1.19758
Aggressive brain tumor	Mean	2.8800	1.1600
Aggressive neoplasm	Mean	2.6900	1.5400
Aggressive intraventricular tumor	Mean	4.5200	1.1100
DENT	Mean	3.6200	2.5500
GBM	Mean	4.3738	1.4542
	Std. Deviation	1.66049	.67892
Glioma	Mean	5.1540	3.6980
	Std. Deviation	2.44954	2.61565
Granuloma	Mean	4.0900	1.7800
Haemorrhagic neoplasm	Mean	2.6500	1.7300
High grade glioma	Mean	7.5800	2.7950
	Std. Deviation	0.69296	.81317
High grade neoplasm	Mean	3.8800	1.3100
Inflammatory	Mean	4.8800	1.5300
Intracranial metastasis	Mean	2.4100	0.9900
Low grade glioma	Mean	3.045	1.77
	Std. Deviation	1.58076	1.09
Lymphoma	Mean	4.4367	0.5933
	Std. Deviation	2.01793	0.48346
Lymphoma/Glioma	Mean	3.7000	0.6900
Malignant cerebellar + metastasis	Mean	4.6700	1.9200
Malignant meningioma	Mean	3.7100	3.9000
Meningioma	Mean	3.9017	2.3117
	Std. Deviation	2.31912	2.76280
Metastasis	Mean	3.5529	2.0643
	Std. Deviation	1.27350	0.64059
Neoplastic process	Mean	4.6718	1.8973
	Std. Deviation	2.52104	1.52805
Neoplastic process/Clivel chordoma	Mean	4.2400	1.2300
Polycystic astrocytoma	Mean	3.3650	1.8000
	Std. Deviation	2.35467	0.73539
Primary brain tumour	Mean	2.7000	1.2800
Radiation necrosis \PNET	Mean	1.0300	2.0400
	Std. Deviation	.	.
Tuberculosis granuloma	Mean	2.3500	1.8900
Tuberculoma	Mean	2.5100	1.2000
	Std. Deviation	1.16047	.48497
Tuberculosis glioma	Mean	1.9300	1.4800
Ventriculitis/abscess	Mean	1.0300	0.4000
Total	Mean	3.8204	1.8123
	Std. Deviation	1.89440	1.30016
P values		0.213	0.679

Section B: 100 cases collected respectively from Royal care hospitals

Table (4.13) frequency distribution of gender:

Gender	Frequency	Percent	Valid Percent	Cumulative Percent
Female	46	46.0	46.0	46.0
Male	54	54.0	54.0	100.0
Total	100	100.0	100.0	

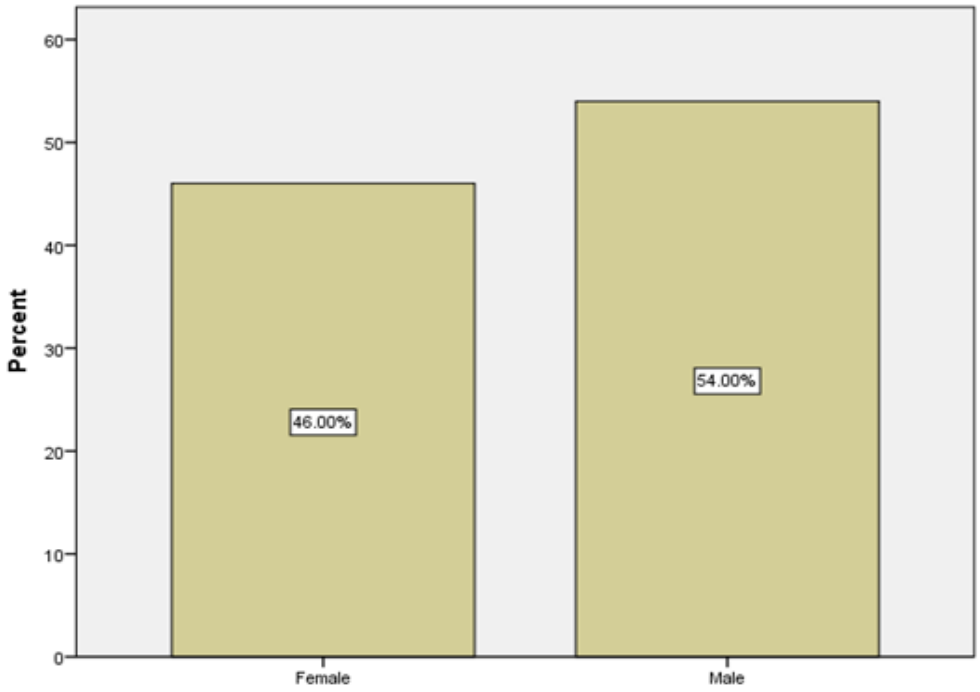

Figure (4.6) frequency distribution of gender

Table (4.14)frequency distribution of age group:

Age group	Frequency	Percent	Valid Percent	Cumulative Percent
2-17	10	10.0	10.0	10.0
18-38	27	27.0	27.0	37.0
39-59	37	37.0	37.0	74.0
60-80	21	21.0	21.0	95.0
more than 80	5	5.0	5.0	100.0
Total	100	100.0	100.0	

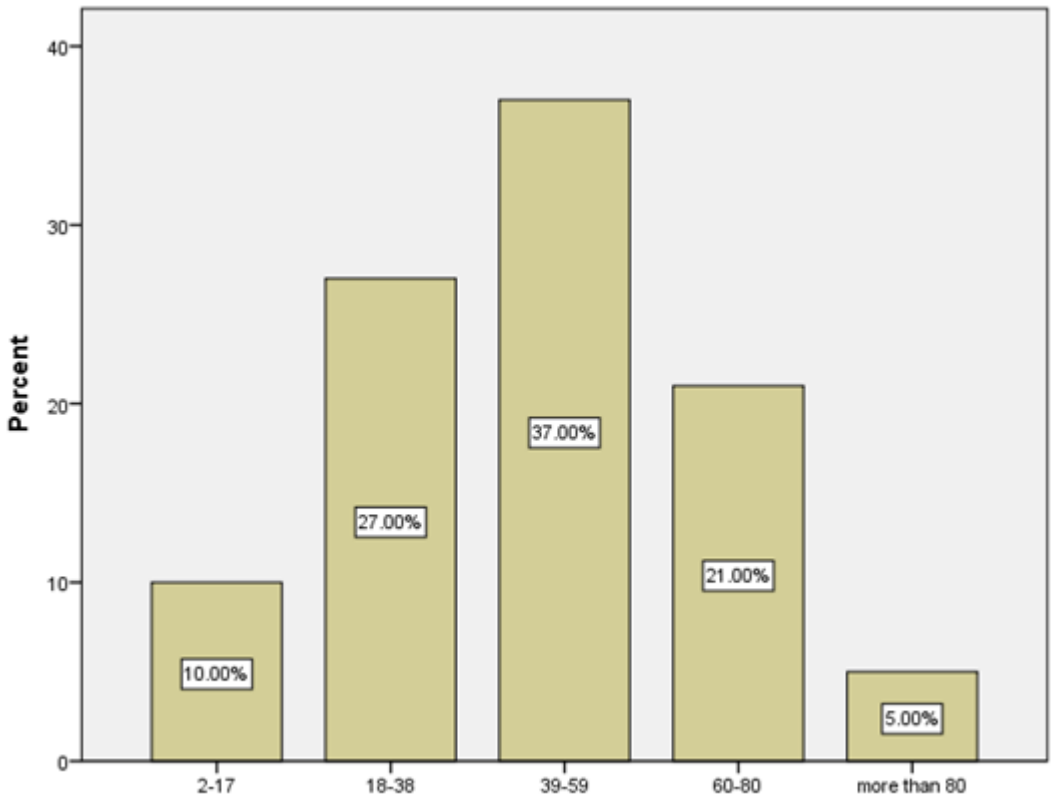

Figure (4.7) frequency distribution of age group

Table (4.15) descriptive statistic for age and Cho/Cr ratio:

Variables	N	Minimum	Maximum	Mean	Std. Deviation
Age	100	2.0	88.0	45.790	20.3937
Cho/Cr ratio	100	1.10	8.00	2.7491	1.26348
Valid N (listwise)	100				

Table (4.16) frequency distribution of MRI finding

MRI finding	Frequency	Percent	Valid Percent	Cumulative Percent
Cerebral Lesion	59	59.0	59.0	59.0
Cerebellar Lesion	9	9.0	9.0	68.0
Brain Stem Lesion	6	6.0	6.0	74.0
Cerebral GBM	6	6.0	6.0	80.0
Cerebral Glioma	4	4.0	4.0	84.0
Extra axial Cerebral Lesion	4	4.0	4.0	88.0
Thalamus Lesion	4	4.0	4.0	92.0
Cerebral+Cerebellar Lesion	2	2.0	2.0	94.0
Basal gangilia Lesion	1	1.0	1.0	95.0
Cerebellar +Brain stem Lesion	1	1.0	1.0	96.0
Cerebellopontine lesion	1	1.0	1.0	97.0
Cerebral Astrocytoma	1	1.0	1.0	98.0
Extra axial Cerebellar Lesion	1	1.0	1.0	99.0
Fourth ventricle Lesion	1	1.0	1.0	100.0
Total	100	100.0	100.0	

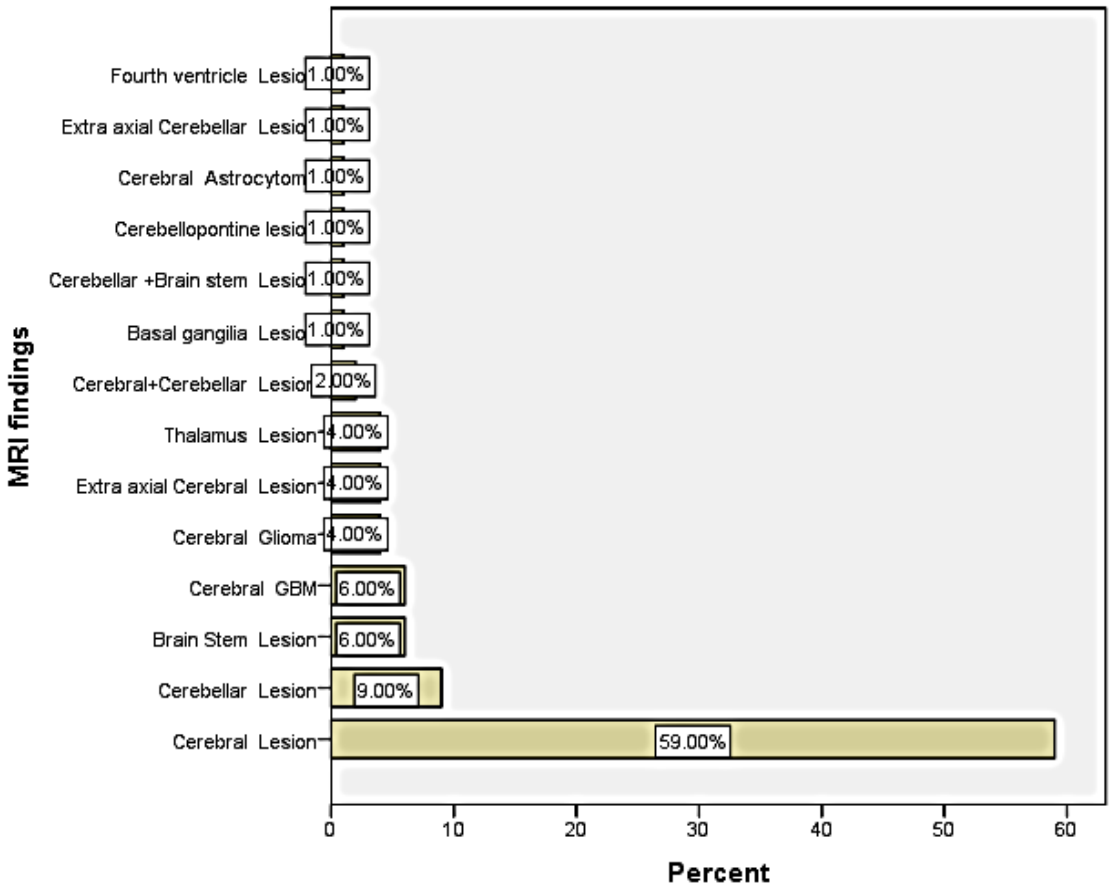

Figure (4-8) frequency distribution of MRI finding

Table (4.17) frequency distribution of NAA:

NAA	Frequency	Percent	Valid Percent	Cumulative Percent
Reduced	86	86.0	86.0	86.0
Normal	10	10.0	10.0	96.0
Absent	4	4.0	4.0	100.0
Total	100	100.0	100.0	

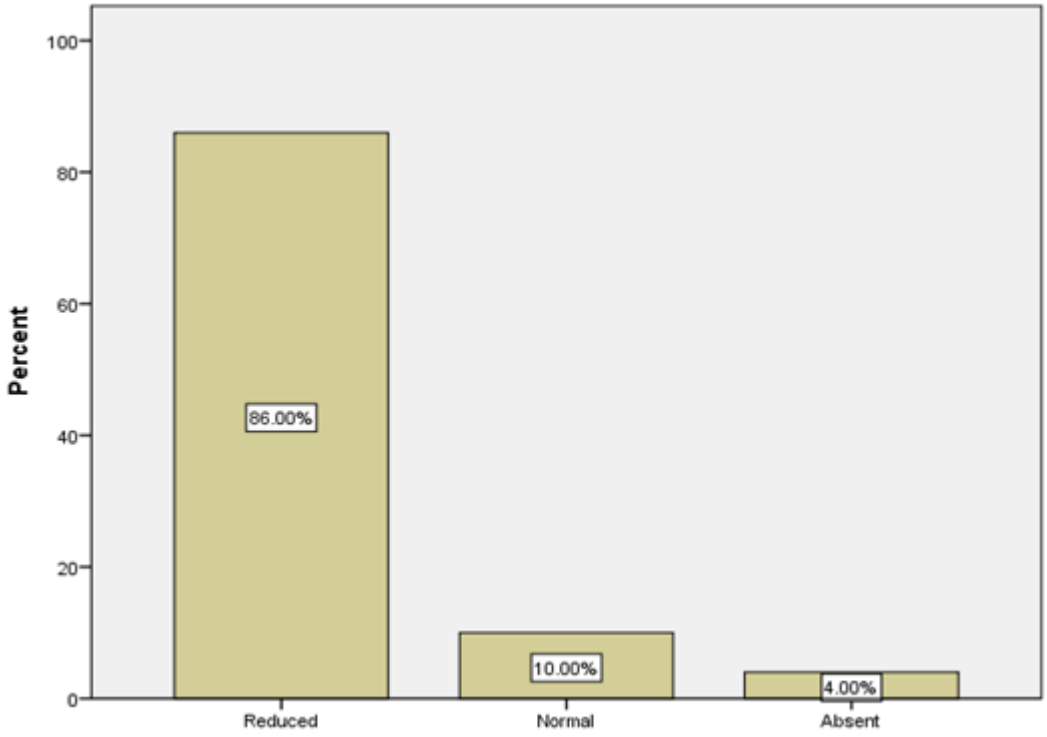

Figure (4.9) frequency distribution of NAA

Table (4. 18) frequency distribution of lipid lactate:

Lipid lactate	Frequency	Percent	Valid Percent	Cumulative Percent
Moderate Elevation	33	33.0	33.0	33.0
Mild Elevation	33	33.0	33.0	66.0
Normal	20	20.0	20.0	86.0
Sky high peak	9	9.0	9.0	95.0
Normal +Alanine peak	5	5.0	5.0	100.0
Total	100	100.0	100.0	

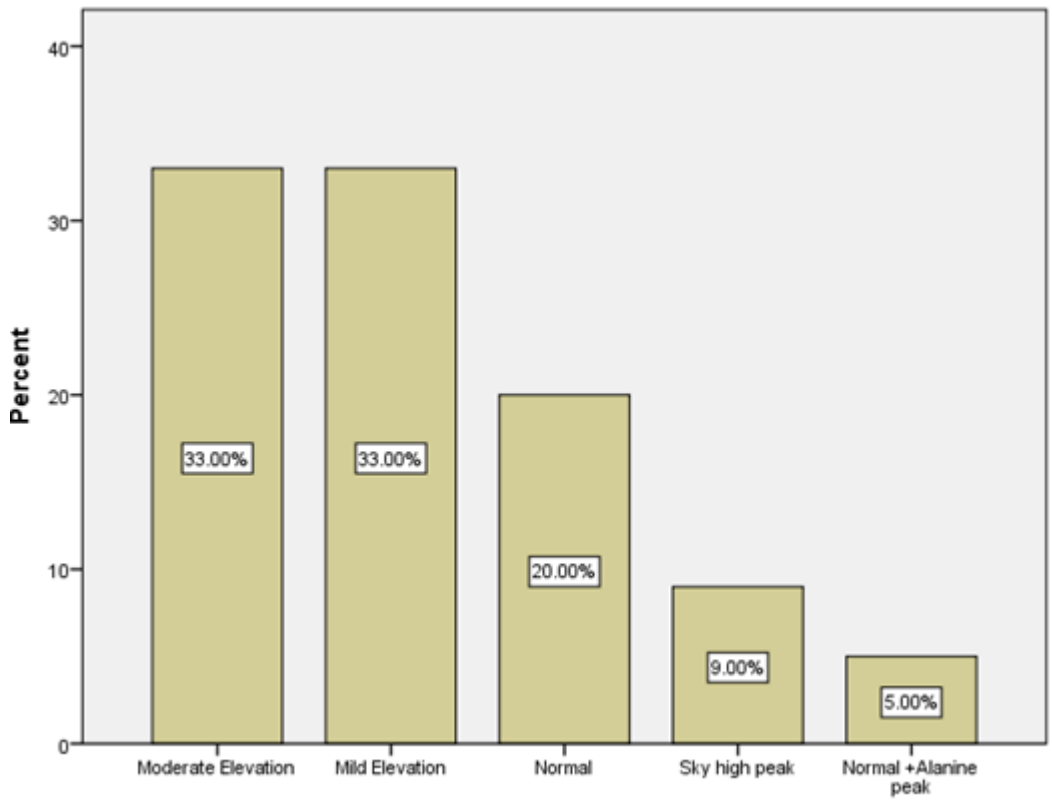

Figure (4.10) frequency distribution of lipid lactate

Table (4.19) frequency distribution of MRS finding:

MRS finding	Frequency	Percent	Valid Percent	Cumulative Percent
Low grade glioma	18	18.0	18.0	18.0
High grade glioma	12	12.0	12.0	30.0
GBM	8	8.0	8.0	38.0
Gliomatosis cerbri	5	5.0	5.0	43.0
Granuloma	5	5.0	5.0	48.0
Meningioma	5	5.0	5.0	53.0
Metastasis	5	5.0	5.0	58.0
TB Granuloma	5	5.0	5.0	63.0
Glioma	4	4.0	4.0	67.0
Low grade glioma DENT	4	4.0	4.0	71.0
Focal encephalitis	3	3.0	3.0	74.0
Low grade tumor	3	3.0	3.0	77.0
Metastasis or lymphoma	3	3.0	3.0	80.0
High grade astrocytoma	2	2.0	2.0	82.0
Low grade ependymoma	2	2.0	2.0	84.0
Neoplastic process	2	2.0	2.0	86.0
Granuloma or Neurological cyst	1	1.0	1.0	87.0
Granuloma, Infection or abscess	1	1.0	1.0	88.0
High grade tumor	1	1.0	1.0	89.0
Inflammatory	1	1.0	1.0	90.0
Inflammatory process likely abscess	1	1.0	1.0	91.0
Intermediate grade glioma	1	1.0	1.0	92.0
Low grade glioma or Lymphoma	1	1.0	1.0	93.0
Lymphoma	1	1.0	1.0	94.0
Malignant neoplastic mass	1	1.0	1.0	95.0
Non neoplastic lesion	1	1.0	1.0	96.0
Oligodendroglioma	1	1.0	1.0	97.0
Recurrence high grade Astrocytoma	1	1.0	1.0	98.0
Recurrence tumor	1	1.0	1.0	99.0
TB Granuloma or Abscess	1	1.0	1.0	100.0
Total	100	100.0	100.0	

Table (4.20) Summary of MRS finding:

Finding on MRS	Frequency	Percent	Valid Percent	Cumulative Percent
Low grade glioma	32	32.0	32.0	32.0
High grade glioma	31	31.0	31.0	63.0
Inflammatory	19	19.0	19.0	82.0
Meningioma	5	5.0	5.0	87.0
Metastasis	5	5.0	5.0	92.0
Metastasis or lymphoma	2	2.0	2.0	94.0
Recurrence tumor	2	2.0	2.0	96.0
Intermediate grade glioma	1	1.0	1.0	97.0
Low grade glioma or lymphoma	1	1.0	1.0	98.0
Lymphoma	1	1.0	1.0	99.0
Metastasis or Lymphoma	1	1.0	1.0	100.0
Total	100	100.0	100.0	

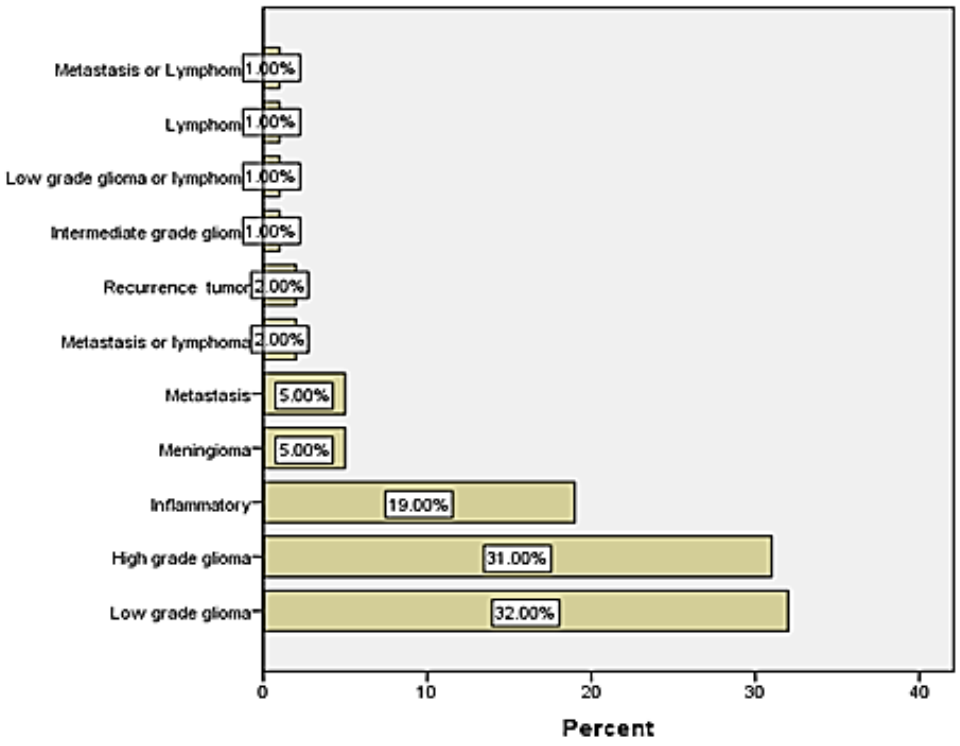

Figure (4.11) Summary of MRS finding

Table (4.21) cross tabulation NAA and MRS finding

MRS finding	NAA			Total
	Absent	Normal	Reduced	
Focal encephalitis	0	0	3	3
GBM	0	0	8	8
Glioma	0	0	4	4
Gliomatosis cerbri	0	0	5	5
Granuloma	0	3	2	5
Granuloma or Neurological cyst	0	1	0	1
Granuloma, Infection or abscess	0	0	1	1
High grade astrocytoma	1	0	1	2
High grade glioma	0	0	12	12
High grade tumor	0	0	1	1
Inflammatory	0	0	1	1
Inflammatory process likely abscess	0	0	1	1
Intermediate grade glioma	0	0	1	1
Low grade ependymoma	0	1	1	2
Low grade glioma	0	1	17	18
Low grade glioma DENT	0	1	3	4
Low grade glioma or Lymphoma	0	0	1	1
Low grade tumor	0	1	2	3
Lymphoma	0	0	1	1
Malignant neoplastic mass	0	0	1	1
Meningioma	2	1	2	5
Metastasis	0	0	5	5
Metastasis or lymphoma	0	0	3	3
Neoplastic process	1	0	1	2
Non neoplastic lesion	0	1	0	1
Oligodendroglioma	0	0	1	1
Recurrence high grade Astrocytoma	0	0	1	1
Recurrence tumor	0	0	1	1
TB Granuloma	0	0	5	5
TB Granuloma or Abscess	0	0	1	1
Total	4	10	86	100
P value 0.005**				

Table (4.22) cross tabulation lipid lactate and MRS finding:

MRS finding	Lipid lactate					Total
	Mild Elevation	**Moderate Elevation**	**Normal**	**Normal +Alanine peak**	**Sky high peak**	
Low grade glioma	11	2	5	0	0	18
GBM	4	4	0	0	0	8
Glioma	1	2	1	0	0	4
Gliomatosis cerbri	0	4	1	0	0	5
Granuloma	1	0	1	0	3	5
High grade glioma	3	6	3	0	0	12
Granuloma ,infection or abscess	0	0	0	0	1	1
High grade astrocytoma	1	1	0	0	0	2
Granuloma or Neurological cyst	1	0	0	0	0	1
High grade tumor	0	0	1	0	0	1
Inflammatory	1	0	0	0	0	1
Inflammatory process likely abscess	0	1	0	0	0	1
Intermediate grade glioma	1	0	0	0	0	1
Low grade ependymoma	0	0	2	0	0	2
Focal encephalitis	0	3	0	0	0	3
Low grade glioma DENT	1	0	3	0	0	4
Low grade glioma or Lymphoma	1	0	0	0	0	1
Low grade tumor	3	0	0	0	0	3
Lymphoma	0	1	0	0	0	1
Malignant neoplastic mass	1	0	0	0	0	1
Meningioma	0	0	0	5	0	5
Metastasis	1	4	0	0	0	5
Metastasis or lymphoma	0	3	0	0	0	3
Neoplastic process	1	1	0	0	0	2
Non neoplastic lesion	0	0	1	0	0	1
Oligodendroglioma	1	0	0	0	0	1
Recurrence high grade Astrocytoma	0	0	1	0	0	1
Recurrence tumor	0	0	1	0	0	1
TB Granuloma	0	1	0	0	4	5
TB Granuloma or Abscess	0	0	0	0	1	1
Total	33	33	20	5	9	100
P value 0.000**						

Table (4.23) compare Cho\ Cr ratio with MRS finding:

MRS Finding	Mean± Std. Deviation
High grade glioma	4.04±.88
GBM	4.73±1.68
Glioma	3.12±.55
Gliomatosis cerbri	2.54±.35
Granuloma	1.36±.28
Granuloma or Neurological cyst	1.20
Granuloma, Infection, or abscess	1.3000
High grade astrocytoma	3.60±.84
Focal encephalitis	1.50±.17
High grade tumors	4.30
Inflammatory	1.70
Inflammatory process likely abscess	4.10
Intermediate grade glioma	3.70
Low grade ependymoma	2.55±.77
Low grade glioma	2.09±.48
Low grade glioma DENT	1.97±.42
Low grade glioma or Lymphoma	1.90
Low grade tumors	2.26±.47
Lymphoma	3.70
Malignant neoplastic mass	3.10
Meningioma	2.16±.72
Metastasis	2.86±.78
Metastasis or lymphoma	4.00±1.21
Neoplastic process	2.65±.77
Non neoplastic lesion	1.10
Oligodendroglioma	2.40
Recurrence high grade Astrocytoma	4.30
Recurrence tumor	3.00
TB Granuloma	1.42±0.20
TB Granuloma or Abscess	1.90
Total	2.74±1.26
P value 0.000	

Chapter Five

Discussion, Conclusion and Recommendations

Chapter Five

Discussion, Conclusion and Recommendations

5.1 Discussion:

Brain lesion are major health problem that increases annually. tumors grading is important for the determination of appropriate treatment strategies .despite the excellent soft tissue contrast provided by MRI, but this modality define lesion type and tumor grade are limited so MR spectroscopic imaging (MRS) provides metabolic information regarding the tissue under study, complementing the anatomic information obtained with conventional MRI.

MRS is non invasive technique limits the use of established invasive diagnostic approaches such as brain biopsy (a heavily invasive technique), which is the gold standard for evaluating brain tumor (Sibtain, et al, 2007)

MRS complements the MRI for characterization of lesion. While the MRI uses signals from hydrogen protons to form anatomic images, the proton MRS uses this information to determine the quantity of brain metabolites such as N-acetyl aspartate (NAA),choline (Cho), Creatine (Cr), lipid ,Alanine and lactate, MR spectroscopy was proven to be a useful imaging tool to discriminate between various brain lesions agree with (Aydın, et al, 2019).

This study was carried out to describe the spectrum of Magnetic Resonance in brain lesions and to show its diagnostic importance in differentiating neoplastic, nonneoplastic lesions. show the importance of MRS in differentiating of the tumor type , detection of the tumor grade, characterize and evaluate the lesion using metabolites' values and assess the types, NAA ,Cho\Cr ratio, NAA/Cr ratio and lipid lactate results and correlate MRS findings with previous studies (Majós, *et al.*, 2009).the data has been collected from 200 patients(male & female) at any age from Khartoum - Sudan ,diagnostic department record system MRI PACS of Almoalem medical city hospital (group A) and Royal care international hospital (group B), which is doing MRI & MRS for investigation of brain lesions. The data has been collected using standard data

sheet including patient gender, age, location of the tumors , MRI&MRS finding during the period from September 2017 to march 2020.

This was a descriptive quantitative an observational cross -sectional study of 200 patients Male 108 (54%) and 92 female (46%), divided through tow groups. Group (A) included 100 patients, incidence of brain lesion was higher in males than females (54% vs. 46%), male: female ratio is (1: 0.85), as shown in figure (4.1) the mean age 43.75 years. The most affected age group was 51-61 years and 18-28 years followed by 40-50 years than 62-72 years (26%, 21%,17%, and 13% respectively) the rate of occurrence is lower in old age1%, as shown in table (4-2). This study was achieved by the evaluation of two metabolite ratios– Cho/Cr and NAA/Cr, NAA and lipid /lac .The study found that the Cho/Cr ratio was 3.76±1.89, while the mean NAA/Cr ratio was 1.81± 1.30, while. The minimum Cho/Cr was 0.65 and a maximum of 10.98, while the minimum NAA\ Cr was 0.08, the maximum was 7.78, (table 4-3). The mean Cho/Cr ratio were higher in GBM (glioblastoma multiform) followed by lymphoma, neoplastic process, glioma, meningioma then DNET, Mets and astrocytoma respectively (4.37 ± 1.66, 4.25 ±1.68, 4.16 ± 2.09, 3.88 ± 2.22, 3.87 ± 2.11, 3.62 ± 0.00, 3.55 ±1.23, 3.36 ± 2.35), while Cho/Cr ratios were lower in radiation necrosis and inflammatory process (1.03 ±0.00 and 1.00 ± 0.00 respectively). NAA/Cr ratio yielded lower values in lymphoma (0.61±0.39), followed by tuberculoma, inflammation and GBM respectively (1.20± 0.48, 1.40±0.00 and 1.45±0.6), as shown in table (4.4).Abscess had lower Cho/Cr (1.71± 0.73) than NAA/Cr (1.85 ±1.28), Radiation necrosis had higher NAA/Cr (2.04 ± 0.00) and very lower Cho/Cr (1.03 ± 0.00) compared to GBM, as shown in Table (4-4). Neoplastic brain lesions caused high Cho/Cr ratio and low NAA/Cr, while nonneoplastic such as abscess and inflammation have less Cho/Cr ratios compare to neoplastic one. A significant difference was found between neoplastic and nonneoplastic brain lesions concerning the Cho/Cr ratio ($p < 001$), while in NAA/Cr ratio no significant difference found between them ($p > 0.05$). In contrast in neoplastic

lesions the Cho/Cr ratio is extremely high compared to nonneoplastic one, while NAA/Cr had not significant different compared to non neoplastic lesions as shown in Table (4-5). It was found that the most prevalent brain tumor diagnosed by MRS was GBM 24%, followed by glioma 14%, then neoplastic process 11% then Mets, meningioma, lymphoma, and tuberculoma were less frequent as shown in figure (4-9).MR spectroscopy was proven to be a useful imaging tool to discriminate between various brain lesions (Aydın et al. 2019). In our study, MRS improved the accuracy of assessing the neoplastic and non neoplastic brain lesions. The present study revealed that GBM was the most common brain lesion, followed by glioma and the neoplastic process, then Mets, meningioma, abscess, and lymphoma It was found that patients with GBM have the highest value of the Cho/Cr ratio compared to other brain lesions. In previous studies, it was reported that all brain masses have reduced NAA signals, and have increased Cho, leading to elevated Cho/NAA ratios. The reduction in NAA peak is mainly attributed to the loss, dysfunction, and displacement of the healthy neuronal tissue since NAA metabolite is considered a primary origin of neurons and axons (Barker, 2001; Chae et al 2019; Mcintyre et al. 2012). Tsougos et al. (2012) reported that Cho/Cr and Cho/NAA have significantly differentiated GBM from other intracranial metastases. The present study found that the NAA/Cr ratio was mostly lower in lymphoma, tuberculoma, then GBM, neoplastic process, astrocytoma, Mets, and glioma. It was observed that in high-grade tumors such as GBM and lymphoma, the Cho/Cr ratio was high, and NAA/Cr was low compared to low-grade tumors (glioma). These findings were consistent with Warren, who reported that brain tumors showed elevated Cho/Cr and decreased NAA/Cr ratios indicating loss of integrity of neurons and increased myelin turnover (Warren, 2004) Additionally, several studies determined that the MRS findings of the brain tumors included a marked reduction in NAA, a slight decrease of Cr, and a marked increase of Cho. Similarly, our findings agreed with those results which

reported increased in Cho/Cr ratio and decreased NAA/Cr in brain masses (Wilken et al., 2000; Vuori et al., 2004; Negendank et al., 1996; Butzen et al., 2000; Usenius et al. 1994; Ott et al.1993). In this study NAA is reduced in 93%and absent in 7% of cases table (4-6) a significant correlation between NAA and MRS findings P value -0.011. , as shown in table (4.10) , 45% of the lesion causes moderate elevation of lipid lactate, 31% mild elevation while in 21 % the lipid lactate is normal and in 3% there is normal lipid lactate and alanine peak seen in cases of meningioma, as shown in table (4.7). A significant correlation between lipid lactate and MRS finding P value -0.001, as shown in table (4.11) , the non neoplastic brain lesions such as abscess, inflammatory process , observed to yield lower values of the Cho/Cr ratio compared to neoplastic lesions. Alberto Surur et al. 2010 found that in most cases of inflammatory lesions, a slight elevation in the Cho peak was noted while the NAA peak remained slightly reduced (Alberto Surur et al 2010). Attia et al. (2020) reported metabolite ratios to have high sensitivity and specificity to differentiate neoplastic from nonneoplastic brain lesions. Another study reported that MRS is accurate in characterizing neoplastic and non neoplastic brain tumors without histopathological analysis (Mania et al. 2018).

Group (B) a total of 100 patients have been selected by using a convenient sampling method. The incidence of brain tumors was higher in males than females (54% vs. 46%) as figure (4.13) ,the age was distributed into five group shown in figure(4,14) the most affected age group in this study is 39-59years 37% followed by 18-38 years 27%, the rate of occurrence is lower in children 10%, as shown in table (4.14). Concerning the evaluation of the tumors by MRI, in 59% stated that it was cerebral lesion, followed by 9% is cerebellar lesion,6% brain stem lesion, 6% cerebral GBM, 4% cerebral glioma, extra axial lesion, thalamus lesion respectively, as shown in figure (4.16).Concerning the evaluation of those tumors in MRS, 86% of tumors showed reduced in NAA, while 10% had normal NAA and in 4% is absent figure (4.17), 33% of the

lesion causes moderate and mild elevation of lipid lactate respectively, while in 20 % the lipid lactate is normal and in 9% there is sky high peak lipid lactate, as shown in table (4.18).There is significant correlation between lipid lactate and MRS finding as it is sky high peak in granuloma, TB granuloma or abscess, normal lipid lactate and alanine peak seen in cases of meningioma, while focal encephalitis may show moderate elevation, and in tumors may be normal or mildly and moderate elevation, p value < 0.01, as shown in table (4.22). The present study showed that also there is significant correlation between NAA and MRS findings p value is 0.005 in table (4.21). It was reduced in most of brain lesion, absent in most case of meningioma, normal in some low grade tumors, as shown in table (4.21).In this study the most brain lesion diagnosed through value of metabolites ratio are low grade and high grade glioma both of them produced low amount of NAA and high Cho, the choline\ creatine ratio is more in high grade than low grade tumors table (4.23), in addition the NAA reduced. The previous studies stated that in MRS of brain tuberculoma peaks of lipids are usually seen due to large lipid fractions. this study MRS finding as it is sky peak lipid lactate in granuloma, TB granuloma or abscess. In tuberculosis bacillus also produced increased choline levels and decreased NAA and Cr. The choline/creatine ratio was greater than 1 in all tuberculoma. MRS identifies tuberculoma and aid in early treatment (Seth et al., 2010; Gutch et al., 2012). Poptani et al. (1995) found that in high-grade gliomas high choline and low or absent N-acetyl-aspartate and creatine, lipid and/or lactate are present, whereas in low-grade gliomas reduced of N-acetyl-aspartate and creatine, increased choline and presence of only lactate. Choline/creatine ratio was significantly higher in high-grade gliomas than in low-grade gliomas p <0.01. Metastasis showed lipid and lactate, whereas choline was visible in only four cases. In the infective masses, pyogenic abscesses demonstrate resonances only from cytosolic amino acids, lactate, alanine, and acetate; and tuberculoma showed only lipid resonances (Poptani, et al., 1995). MRS complements the MRI for

characterization of lesion. While the MRI uses signals from hydrogen protons to form anatomic images, the proton MRS uses this information to determine the quantity of brain metabolites such as N-acetyl aspartate (NAA), choline (Cho), Creatine (Cr), and lactate. Brain lesion can caused reduced, markedly reduced or absent N-acetyl aspartate (NAA) with increased choline (Cho), elevated lactate (LAC) and lipid peaks (Byrd et al., 1996; Shetty et al., 2014).

5.2Conclusion

MR Spectroscopy showed early change in tissue especially in brain because it is detect the biochemical changes in tissue, this makes MRS best modalities for detecting brain lesion. It's provides complementary information about cellular metabolism, allows differentiating the brain tumors from abscess, Characterization of brain lesion, allows optimizing the guided biopsy as well as to differentiating recurrent tumor from a necrosis, the MR spectroscopy has a great interest in the exploration and therapeutic strategies of brain tumors, Magnetic Resonance Spectroscopy (MRS) is now a day's considered as a main investigation modality in the clinical routine jointly with conventional Anatomical and functional magnetic resonance imaging MRI For studying brain Lesion, MRS allowed the non invasive differentiation between high-grade and low grade tumors. Cho/NAA, Cho/Cr as well as NAA/Cr / ratios were the most reliable in determining the tumor grade. MR spectroscopy techniques further improve, more features of MR spectra can be quantified tools for pre operative diagnoses and for characterization of tumor metabolism in individual patients, MRS can also be performed in clinical practice to guide the neurosurgeon into the most aggressive part of the lesions or to avoid unnecessary surgery, which may furthermore decrease the risk of surgical morbidity, the technique is very sensitive to in homogeneities in the magnetic field and requires careful manual adjustment to ensure field uniformity. Artifacts can arise from braces on teeth or proximity to sinuses. If any bone is included in the voxel, it can cause artifacts due to the lipid signal arising from bone marrow, the small lesion like granuloma need magnetic resonance spectroscopic imaging (MRSI) rather than Single-voxel spectroscopy (SVS) because of the smaller voxel size and limitations in the length of time of image acquisition.

MR Spectroscopy is a highly sensitive tool, however its specificity is relatively high in differentiating neoplastic from nonneoplastic lesions must

be do the tow ratio Cho/Cr and NAA/Cr for better diagnosis , this values makes MRS adequate as the definitive diagnostic tool. MRS metabolic ratios (Cho/Cr and Cho/NAA) can be used to grade and differentiate gliomas. Ratios from 1.5 to 2 were suggested to be as low grade glioma and ratios higher than 2 were suggested to be high grade glioma or metastasis. Metastases were similar to high grade glioma in its readings, the diagnostic strategy was evaluated by MRS are useful as additional Imaging techniques for establishing the differential diagnosis between brain metastases and brain tumors by do curve in the peripheral area of the tumor and show curve like normal brain curve, for cases of brain metastases, Meningioma can be diagnosed by MRI images and MRS should added to routine MR imaging as it provides greater information concerning tissue characterization than what is possible with MR imaging studies alone, specific Alanine for Meningioma MRS were proposed to improve the diagnosis and characterizing of brain lesions with Long TE of (2000/136ms) where the signal from most metabolites in the brain is lost except that of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate, alanine need short TEs of (2000/20 -35ms) those allow for identification of many other metabolites Lipids, lactate, myo-inositol, glutamate, and glutamine were used for diagnosis and characterizing of some brain lesions, this Study concern with MRS finding and is sensitive differentiate between the benign and malignant lesions which difficult or impossible by conventional MRI methods alone ,so MRS is complementary to MRI and the MRS could be used in the Therapeutic follow-up for evaluating the pathological active in brain.

5.3 Recommendations

- We recommend doing MRS routinely in patients with brain lesions to Improve the accuracy of neuro diagnosis and for other benefit in patient Management such as, differentiation between tumor and tumor like lesions, diagnosis of primary and secondary brain tumors and lymphoma, Grading of cerebral gliomas, Treatment planning of gliomas, differentiation between the recurrent / residual tumor and the radiation injury, and other focal intracranial lesions, Magnetic resonant spectroscopy may give completely different information related to brain lesions and save time ,risk and cost.
- We recommend to encouraging more studies to be done in MRS with a Larger sample size and comparison with other imaging and histopathology findings to give us more information about the impact of the new technique .This modality should be considered as an adjunct to conventional imaging rather than replacement for histopathological evaluation. MRS added to conventional MRI helps in tissue characterization of intracranial mass lesions.
- The technique is very sensitive to in homogeneities in the magnetic field and requires careful manual adjustment to ensure field uniformity. Artifacts can arise from braces on teeth or proximity to sinuses. If any bone is included in the Voxel, it can cause artifacts due to the lipid signal arising from bone marrow.
- MRS should be joined with the routine MRI examinations in all suspected brain masses for further assessmentto assess the accuracy of MRS in differentiation and grading of different brain lesion. Also, more cases have to be added for more accurate result.
- Further studies should be done adding biopsy results compare the MRS metabolites ratios to biopsy analysis for better accuracy.

- MRS is also very sensitive to motion. To overcome these limitations of MRS, researchers and clinicians have moved studies to higher field strengths to gain signal-to-noise ratio and to detect additional metabolites more reliably.
- The MRS technique is need very short time for do spectra, limitation is show when do patients sick, an unstable and moving during the investigation.
- The small lesion needs Magnetic resonance spectroscopic imaging (MRSI) rather than Single- voxel spectroscopy (SVS) Because of the smaller voxel size and limitations in the length of time of image acquisition.
- The diagnosis of the tumors types is a accurately done by biopsy which is difficult and invasive and high costly but the majority of patients are poor, so non invasive methods MRS is needed to characterizing the tumors types. Before surgery to put the program of treatment before surgery so that needs to increase diagnostic centers of MRS in Sudan.
- The unavailability of the histopathological results for comparison, because many of our patients don't have the operations yet due to refusal of surgery, poor patients or other problems. Also limitation comes from the small size of sample.

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Appendices

Appendices (A)

Group (A) Almoalem medical city Data collection sheet

No	Age	Sex	Location of lesion	MRI finding	Cho/Cr ratio	NAA/Cr ratio	NAA	Lipid/Lac	MRS finding

Group(B)Royal care hospital Data collection sheet

No	Age	Sex	Location of lesion	MRI finding	Cho/Cr ratio	NAA	Lipid/Lac	MRS finding

Appendices (B)

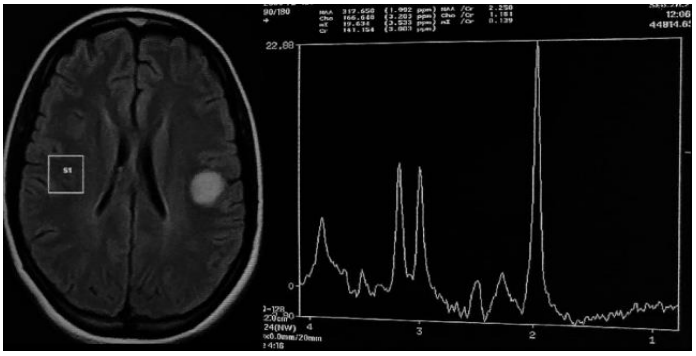


Figure 1 Female, 18years Normal Curve

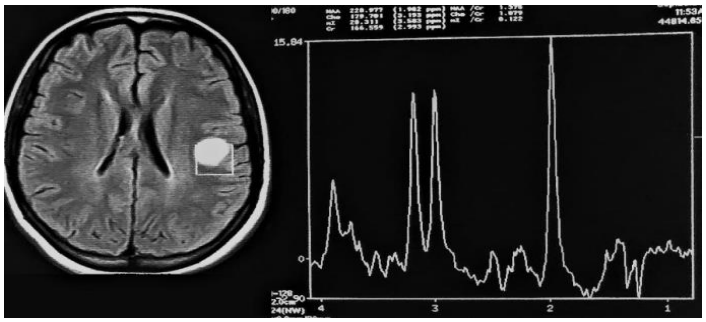


Figure 2 Female, 18year low grade glioma (DNET) , Ch/Cr 1.5, Reduced NAA, Mild elevation lipid/lac

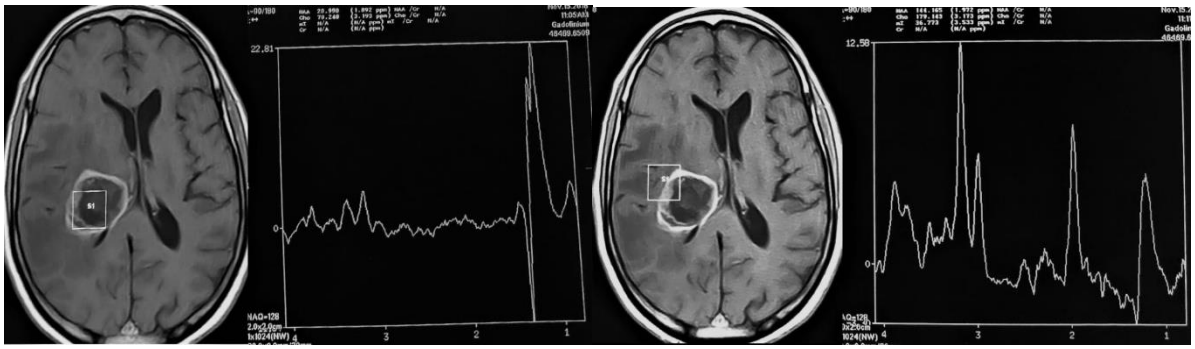


Figure3 **Figure4**

Figure3&4 male 56years glioplastoma multiform Ch/Cr 3.6,Redused NAA, moderate elevation lipid/lac

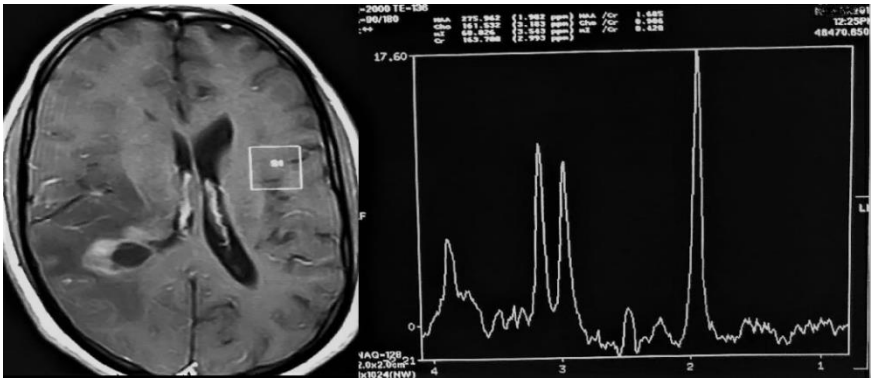
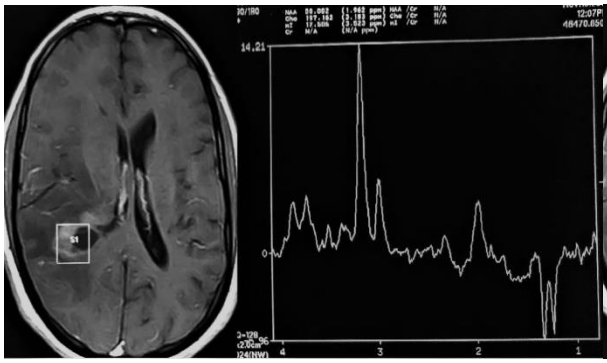


Figure 5 male 39 years Normal Curve



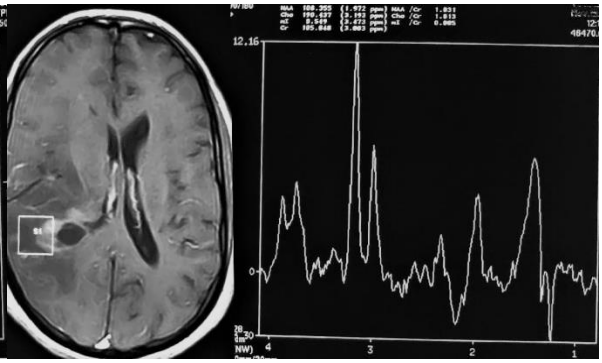
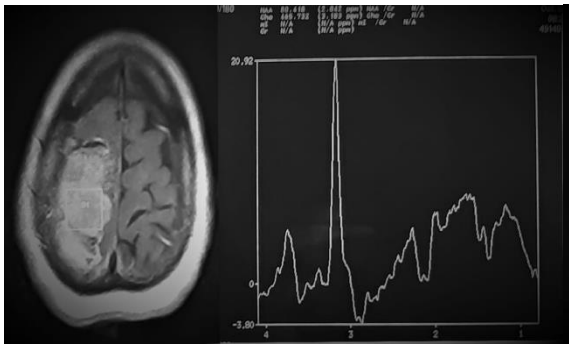


Figure6 **Figure7**

Figure6& Figure7 male 39years gliomatosis cerbri -Infiltrative neoplastic process Ch/Cr 3.14, Reduced NAA, moderate elevation lipid/lac



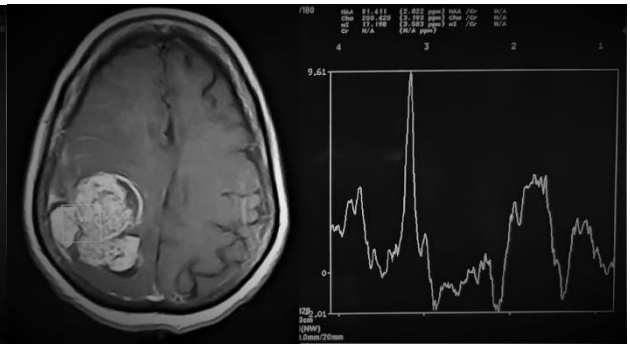


Figure8 **Figure9**

Figure8&9 female 65years Malignant neoplastic Ch/Cr 3.1, Reduced NAA, moderate elevation lipid/lac

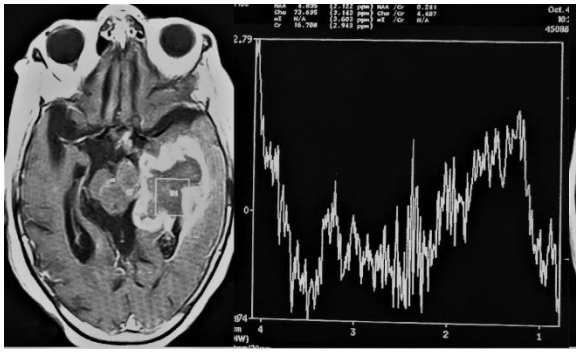


Figure10

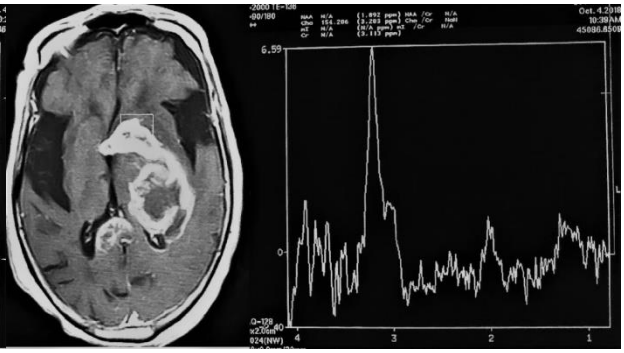


Figure11

Figure10&11female 83years High grade glioma Ch/Cr 4.2, Reduced NAA, mild elevation lipid/lac

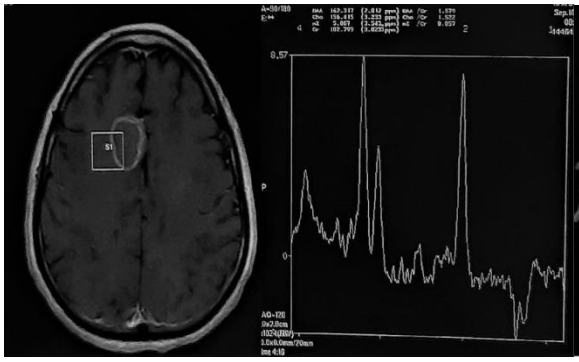


Figure12

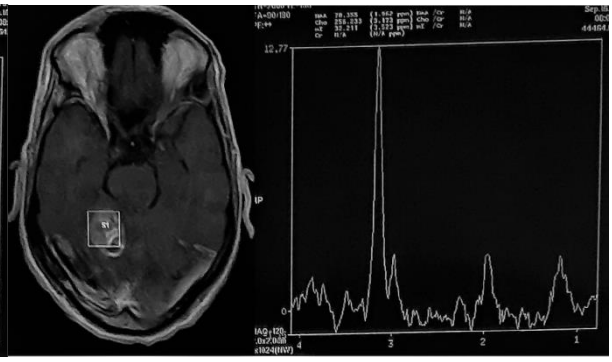


Figure13

Figure12&13male 43years Metastasis Ch/Cr 2.7, Reduced NAA, moderate elevation lipid/lac

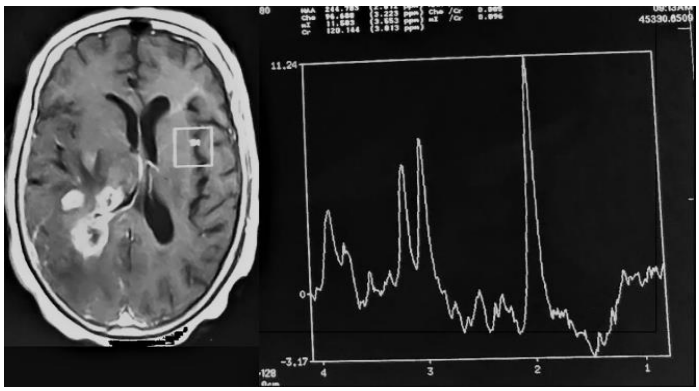


Figure 14 Female, 80years Normal Curve

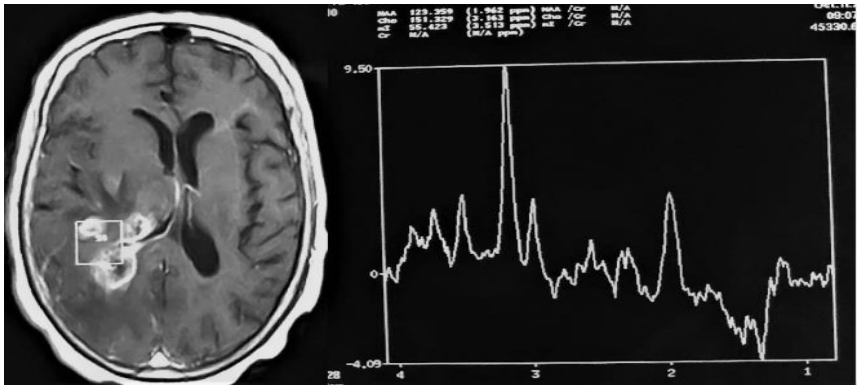


Figure 15 Female, 80years, High grade glioma Ch/Cr 4.7, Reduced NAA, moderate elevation Lipid/lac

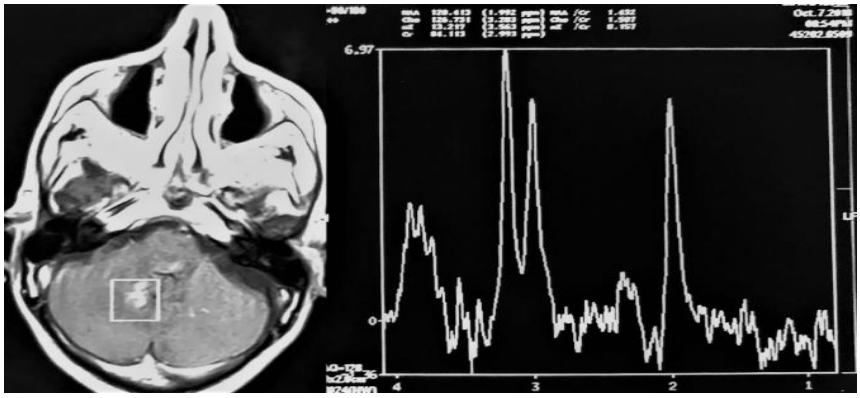


Figure16 male, 65years, Focal encephalitis ,Ch/Cr 1.7, Reduced NAA, moderate elevation Lipid/lac

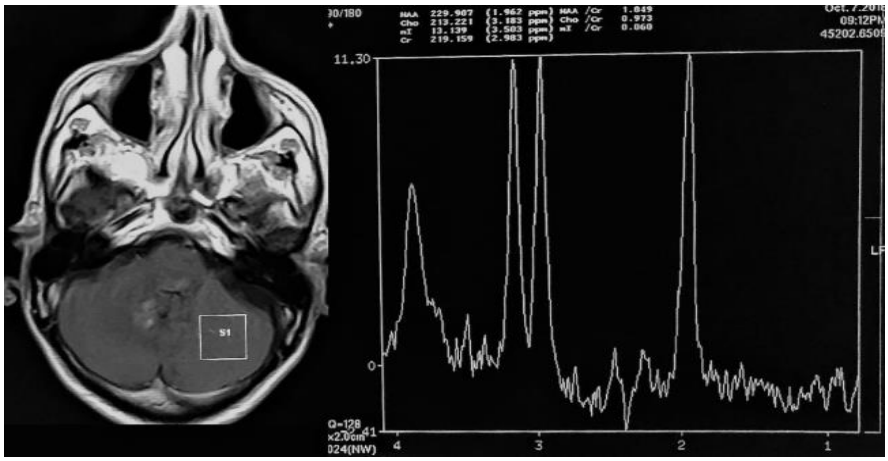


Figure 17 male, 65years Normal Curve

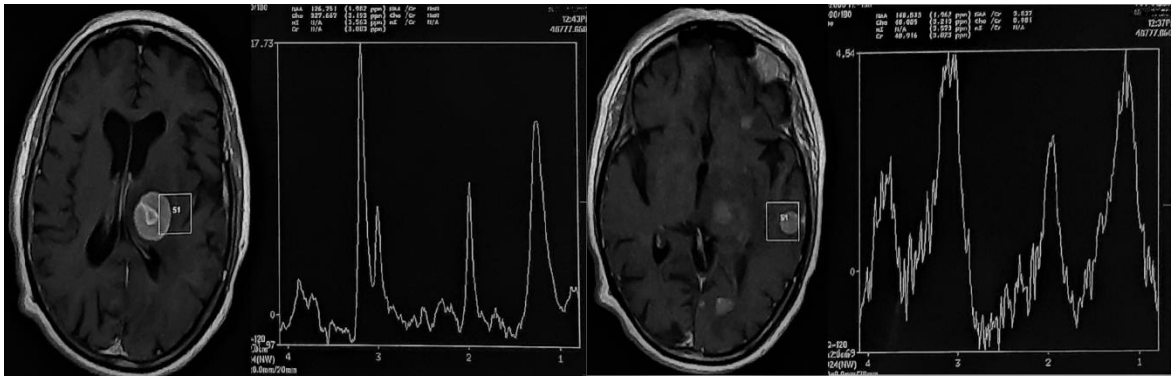


Figure18 **Figure19**

Figure18&19female 70years Metastasis Ch/Cr 2.4, Reduced NAA, moderate elevation lipid/lac

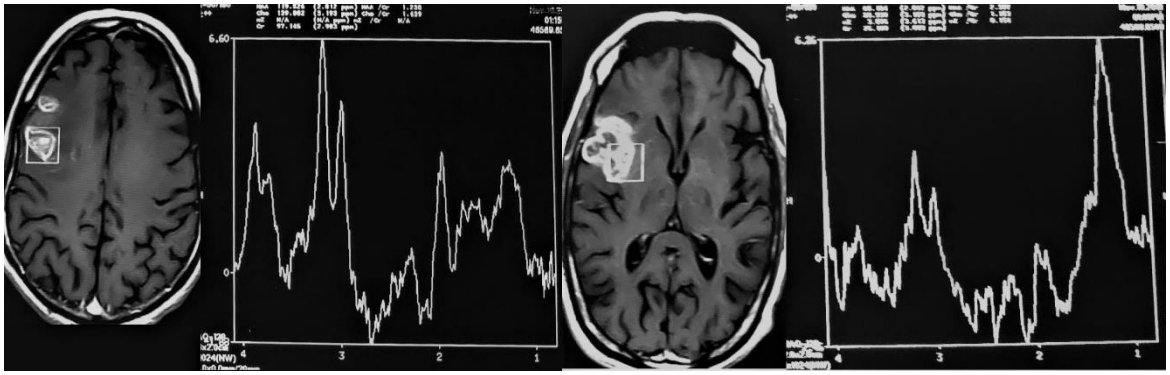


Figure20 **Figure21**

Figure20&21male 54years Focal encephalitis Ch/Cr 1.4, Reduced NAA, moderate elevation lipid/lac

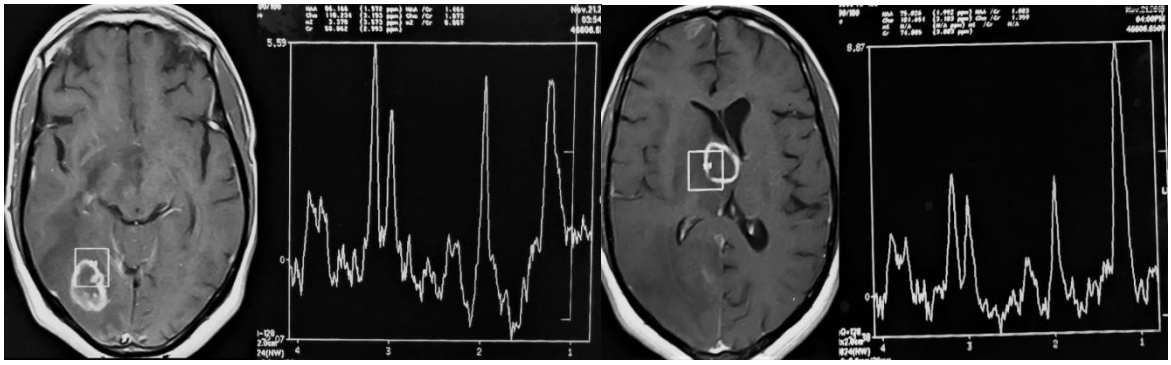
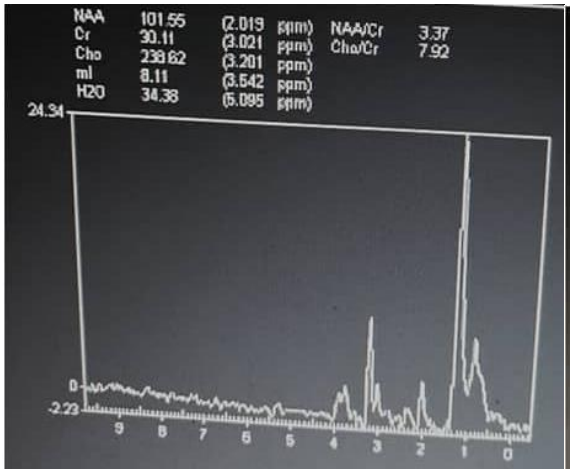


Figure22 **Figure23**

Figure22&23male 30years Metastasis Ch/Cr 1.9, Reduced NAA, moderate elevation lipid/lac



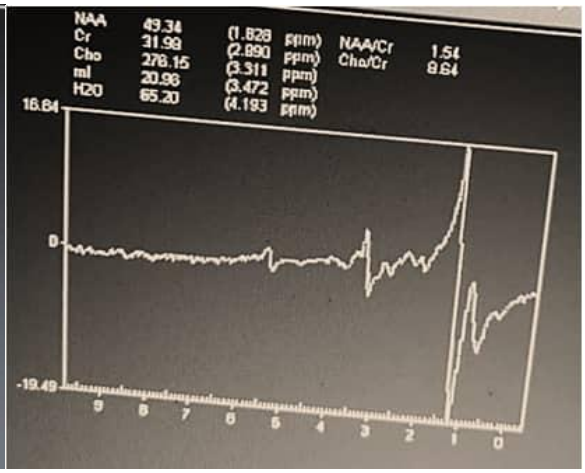
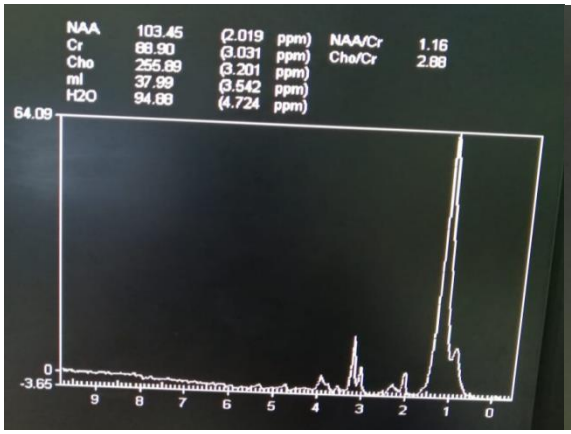


Figure24 **Figure25**

Figure24&25 female 26years High grade glioma, Ch/Cr 7.09, NAA/Cr 3.37, moderate elevation lipid/lac Reduced NAA



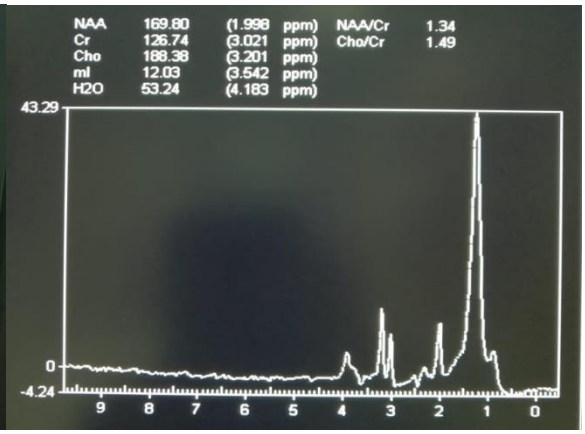
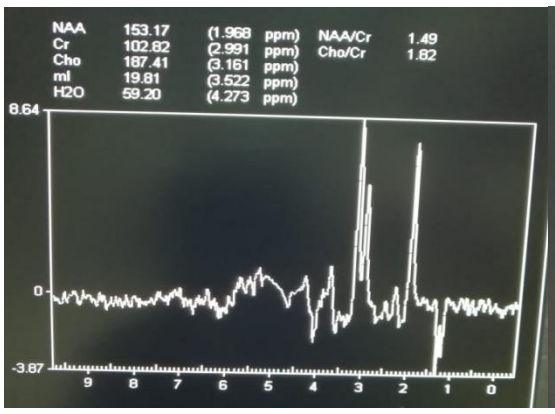


Figure26 **Figure27**

Figure26&27 male 54years Aggressive brain tumor Ch/Cr 2.88 NAA/Cr 1.1 Reduced NAA. Mild elevation lipid/lac



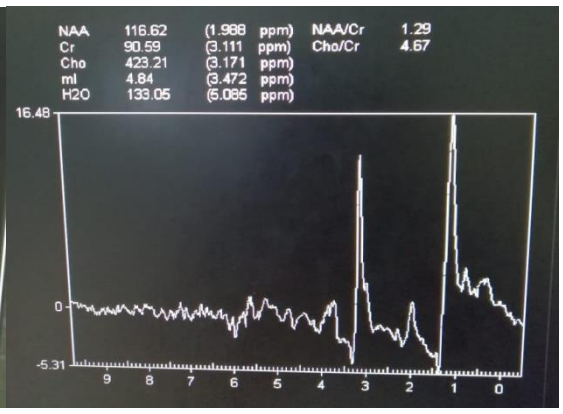


Figure28 **Figure29**

Figure28&29 male 60years malignant Cerebellar +metastasis Ch/Cr 4. 67 NAA/Cr 1.29 Reduced NAA. Moderate elevation lipid/lac.

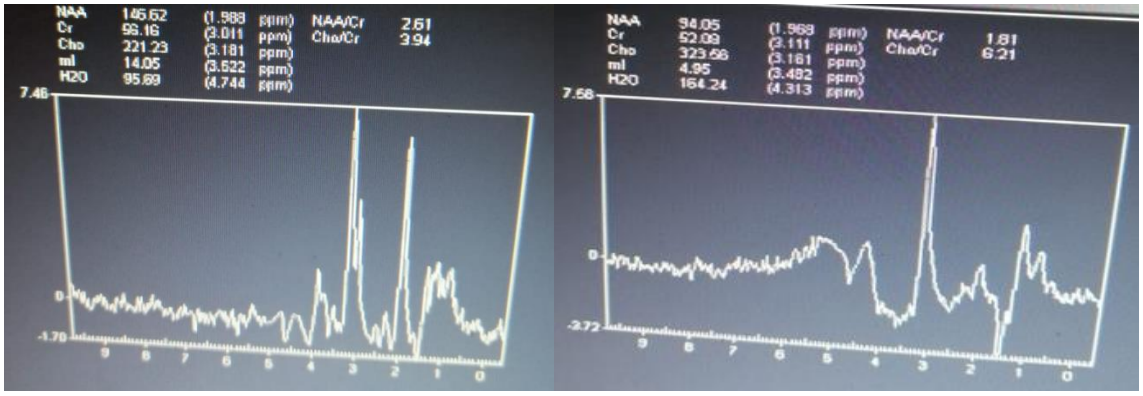


Figure30 **Figure31**

Figure 30&31 female 48years glioplastoma multiform Ch/Cr 3.94 NAA/Cr 2.61 Reduced NAA. Moderate elevation lipid/lac

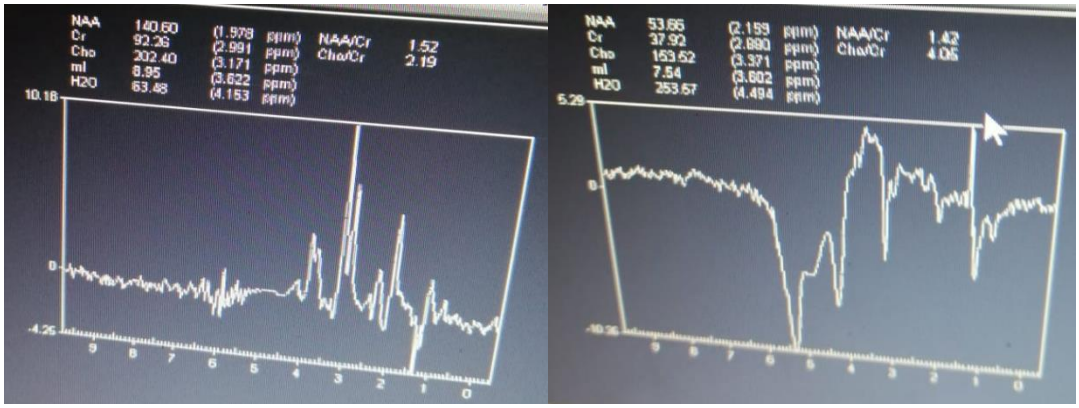


Figure32 **Figure33**

Figure 32&33 male 90years neoplastic process Ch/Cr 4. 05 NAA/Cr 1.42 Reduced NAA. Mild elevation lipid/lac

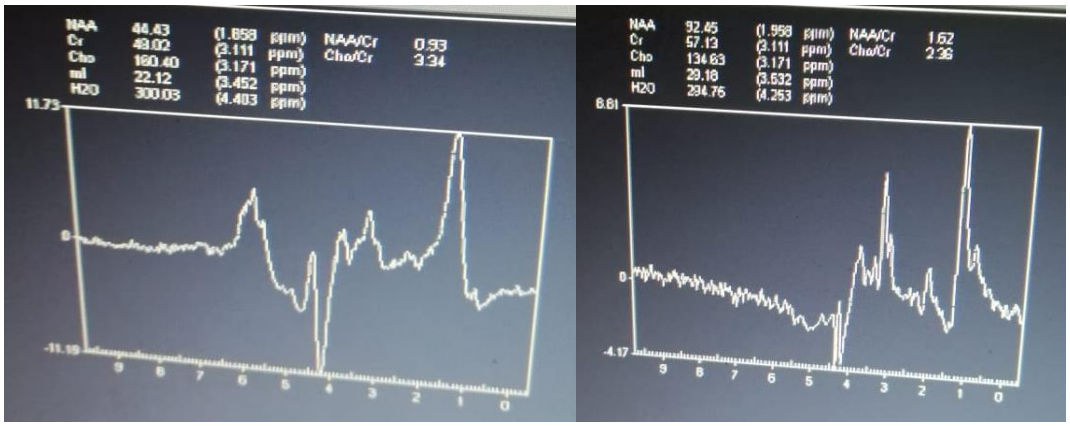
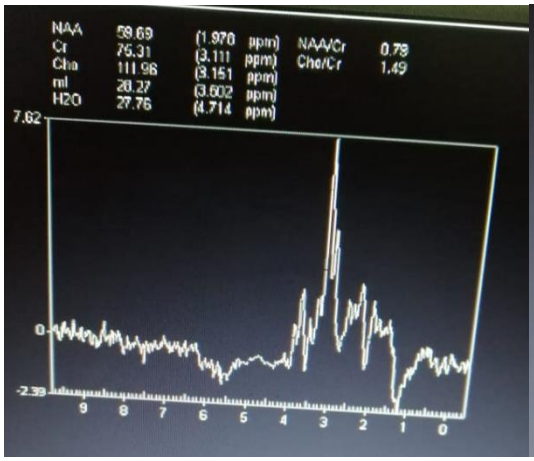


Figure34 **Figure35**

Figure 34&35 male 68years glioplastoma multiform Ch/Cr 3.34 NAA/Cr 0.93 Reduced NAA. Moderate elevation lipid/lac



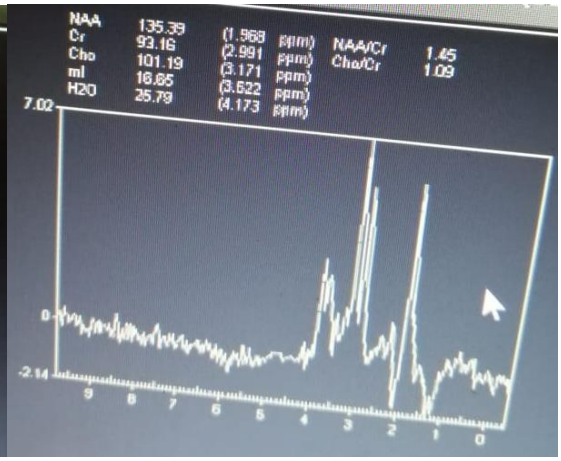
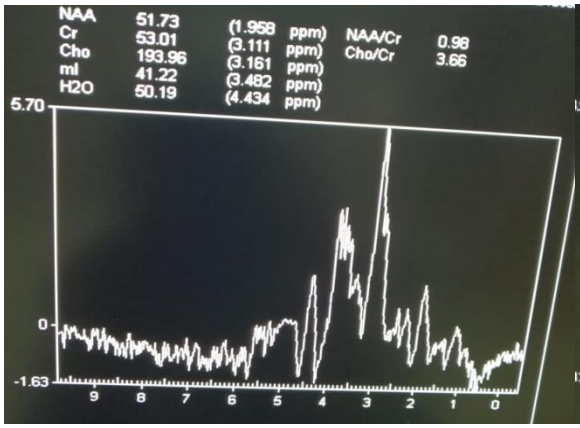


Figure36 **Figure37**

Figure 36&37 female 15years cystic meningioma Ch/Cr 1.49 NAA/Cr 0.79Reduced NAA. Normal lipid/lac + Alanine



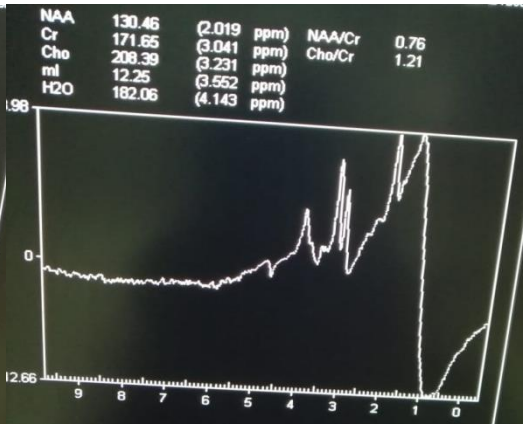
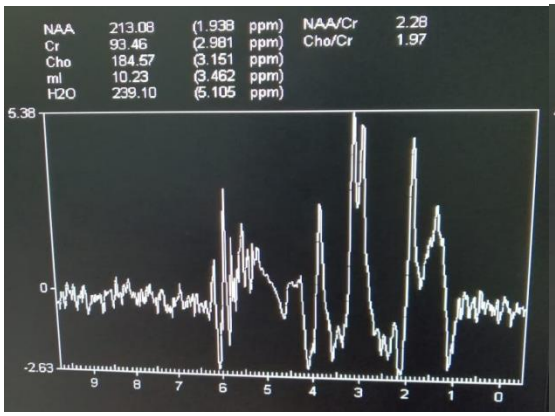


Figure38 **Figure39**

Figure38&39 female 65years Metastasis Ch/Cr 3.66NAA/Cr 0.98 Reduced NAA. Mild elevation lipid/lac



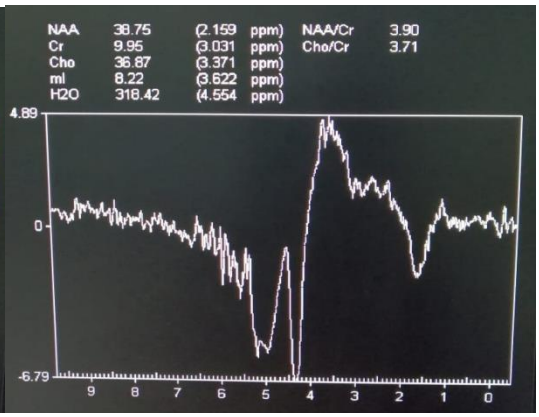
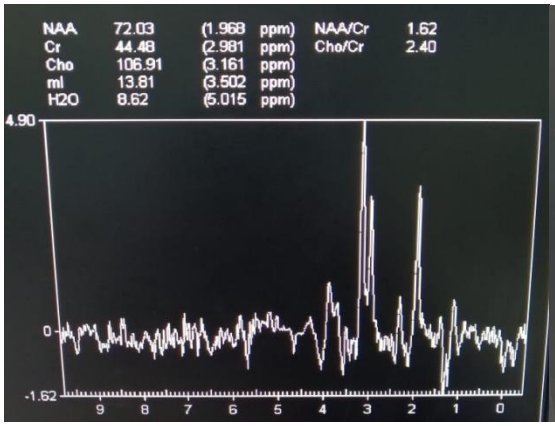


Figure40 **Figure41**

Figure 40&41 male 65years malignant meningioma Ch/Cr 3.71NAA/Cr 3.9Absent NAA. Normal lipid/lac + alanine



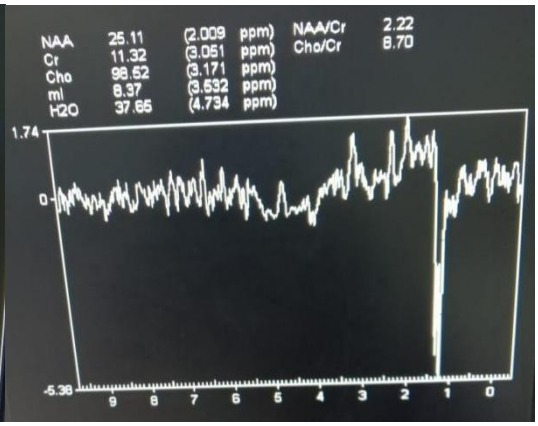
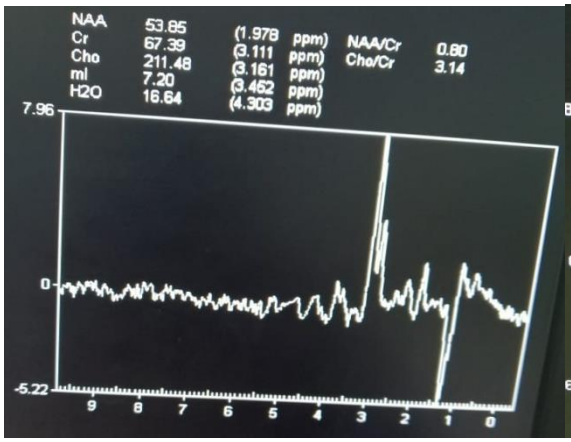


Figure42 **Figure43**

Figure 42&43 male 65years high grade glioma Ch/Cr 8.70 .NAA/Cr 2.22 reduced NAA. Moderate elevation lipid/lac



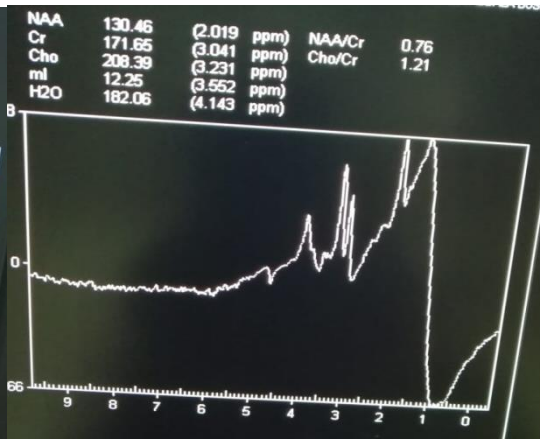
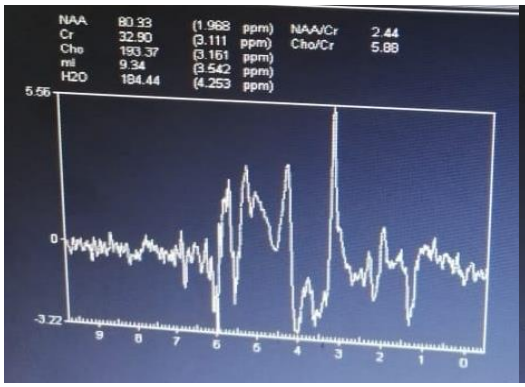


Figure44 **Figure45**

Figure 44&45female 20years Lymphoma Ch/Cr 4.73NAA/Cr 0.68 reduced NAA. Mild elevation lipid/lac



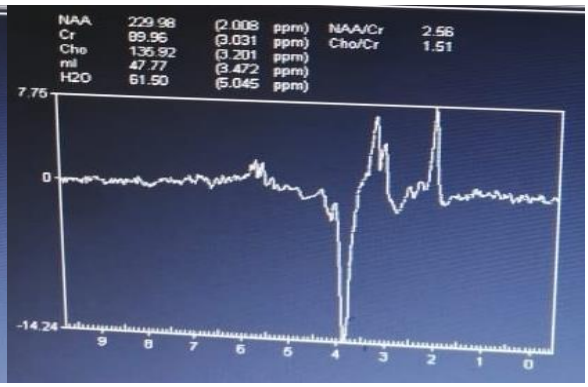
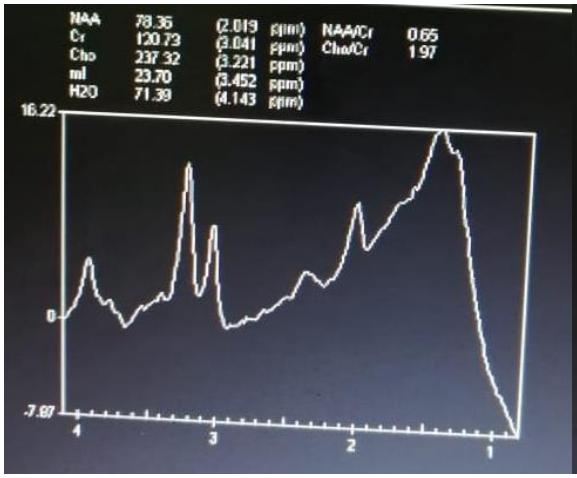


Figure46 **Figure47**

Figure 46&47 male 70years glioplastoma multiform Ch/Cr 5. 88 NAA/Cr 2.44 ,reduced NAA. Moderate elevation lipid/lac



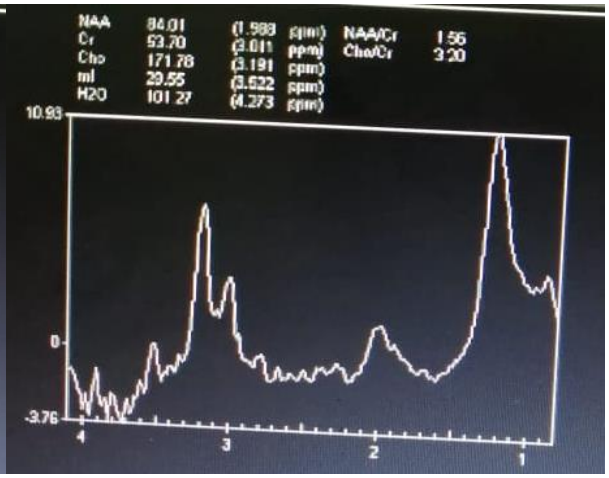
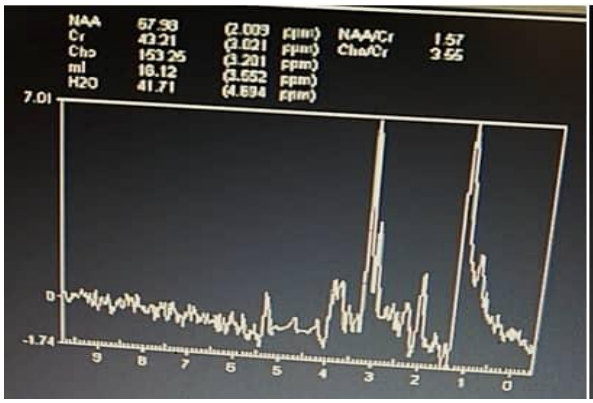


Figure48 **Figure49**

Figure 48&49 female 76years brain Abscess Ch/Cr 3.20 NAA/Cr 1.56 reduced NAA. Mild elevation lipid/lac



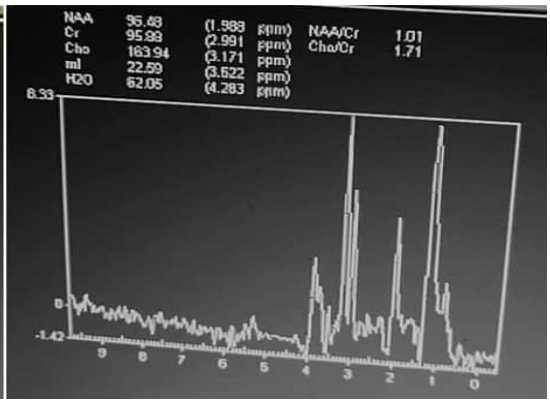


Figure50 **Figure51**

Figure 50&52 female 60years glioplastoma multiform Ch/Cr 3.55 NAA/Cr 1.57 Reduced NAA. Moderate elevation lipid/lac