A Review On The Occurrence Of Brain Tumor in Adults And Pediatrics And The Associated Risk Factors

By

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of
Master's in Biotechnology (MS BIO)

Department of Mathematics and Natural Sciences
Brac University
May 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis/project titled A Review On The Occurrence Of Brain Tumor in Adults and Pediatrics And The Associated Risk Factors submitted by

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Ethics Statement

I hereby declare, I have not performed any immoral or unethical action for the fulfillment of my thesis. I have completed my work remaining whole heartedly sincere, with my utmost dedication and honesty.

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Abstract

Brain tumor is one of the most concerning disorders of modern times, yet comprehensive knowledge on its symptom, risk factors, diagnosis, treatment and post-treatment of both adult and children have not been documented together. Therefore, to investigate the brain tumor symptoms, associated risk factors, methods of diagnosis, treatment, and post treatment rehabilitation for both adults and children and lastly the facility for brain tumors available in Bangladesh related peer reviewed journals and books were screened from databases like ResearchGate, Google Scholar, PubMed, and National Centre for Biotechnology Information. In this review, multiple categories of risk factors that may influence the occurrence of brain tumors became prominent. Gliomas and Medulloblastomas came out as the most common brain tumor in adults and pediatrics respectively. In Bangladesh, cases of Astrocytoma were found to be higher in adults, and low-grade Medulloblastomas in paediatrics. In terms of common symptoms, headaches, seizures, and vomiting stood out to be the most frequent. To conclude, this review aims to help educate people more on brain tumors and increase awareness in this sector. Some people with multiple risk factors do not develop brain tumors while people with no known risk factors might develop brain tumors. Knowing personal risk factors and taking preventative measures toward them will help to make more informed decisions.

Keywords: Brain tumors; symptoms; risk factors; causes; diagnosis; treatment; post-surgery, rehabilitation; paediatrics; Bangladesh

Dedication

I would like to dedicate my work to my family and my husband. They have been my source of inspiration, support, and guidance. They have taught me to be unique, determined, to believe in myself, and to always persevere. I am ever so thankful for them.

Acknowledgement

I would like to take this opportunity to deeply be thankful for my thesis supervisor and MS and BS Biotechnology Program Director & Associate Professor of BRAC University Dr. Munima Haque for her constant mentorship, guidance, constructive insights, and support throughout both my master's degree and thesis journey. I would like to thank her for granting me such an interesting topic to work on and finding underrated links of it with Biotechnology. This would not have been possible without her encouragement and passion.

I would also want to thank my fellow classmate and research assistant of MNS department Shabnoor Binte Dayem for the continuous assistance and advice.

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List of Acronyms

CNS	Central Nervous system
PNS	Peripheral Nervous system
ATPase	Adenosine Triphosphatase
BM	Brain metastases
OS	Overall survival
MHz	Mega hertz
SAR parameter	Sodium Adsorption Ration
IARC	International Agency for Research on Cancer
RF-EMF	Radiofrequency Electromagnetic Field
PM	Particulate Matter
FDG	Fluorodeoxyglucose
mSv	Millisievert
ADL	Activities of Daily Life

Chapter 1

Introduction

Neuroscience, which has traditionally been thought to be a subdivision of biology, has recently proved to be an interdisciplinary science linked closely with various other disciplines such as mathematics, engineering, philosophy, computer science, medicine, etc. [1]. It is the understanding of the nervous system regarding the biological root of consciousness, perception, memory, and learning. Observations about cognitive behavior is linked to the physical processes by neuroscience [2]. Neuroscience is also known as neural science which involves anything to do with the nervous system- the study of how the human nervous system develops, its structure and what it does. They study the cellular, functional, evolutionary, computational, molecular, cellular, and medical aspects of the nervous system thus have a wider scope of fields now compared to before. Whereas neurobiology focuses mainly on the biology of the nervous system [3].

In addition to examining the normal development and activity of the nervous system, neuroscience studies diseases, disorders and injuries that affect parts of the nervous system, how it develops, and how well it functions. There are more than 1,000 disorders of the brain and nervous system including: Degenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Niemann-Pick disease. Musculoskeletal disorders, such as muscular dystrophy and stroke. Injuries, including traumatic brain injury and spinal cord injury as well as how the body processes pain. Cancers, including brain tumors such as paragangliomas. Immune system disorders, such as HIV/AIDS etc. [4].

Human nervous system is considered as the body's command center. It controls movements, thoughts, and our automatic reflexes to the environment. Moreso, it also controls other body processes such as homeostasis, digestion, breathing and sexual

development. Accidents, diseases, toxins, and natural aging causes damage to the nervous system. The greater nervous system is comprised of the central nervous system (CNS), peripheral nervous system (PNS), somatic and autonomic nervous systems. It is one of the most complex systems in the human body and communicates with other body systems to maintain physiologic homeostasis [5].

The human brain is a fragile and complex organ whose postnatal function depends on normal development of the embryo and fetus. It can be said that our brain is the most important part of the body without a doubt. It directs and coordinates actions and reactions [6]. Through the five senses of sight, smell, hearing, touch and taste, the brain receives messages, often many at the same time [7]. The brain examines all stimuli from the internal organs, the surface of the body, the eyes, nose, and mouth. It then responds to these stimuli by modifying body position, limb movements, and the speed at which internal organs function. The brain can also determine mood, awareness, and attention [8].

Any tumor can be described as a solid mass of tissue formed when cells divide uncontrollably. Tumors can be malignant, which are cancerous and can be life-threatening. Tumors can also be benign, which are non-cancerous, but both need treatment. They can affect bones, skin, tissue, organs, and glands [9]. Similarly, brain tumor is a growth of abnormal cells in any part of the brain or skull, including the protective lining, skull base, brainstem etc. As the anatomy of the brain is very complex, with different parts being responsible for dissimilar important nervous system functions, there are 120 different types of tumors that develop in the brain depending on what tissue they arise from [10].

Although the frequency of the brain tumors appears to have increased over the past 30 years, the increase is likely due to the new use of new imaging techniques [11]. The incidence of

central nervous system (CNS) tumors in India ranges from 5 to 10 per 100,000 population with an increasing trend and accounts for 2% of malignancies [12].

The overall incidence of malignant brain tumors varies across different regions of the globe. In 2016, it was estimated that there were 330,000 new cases, 227,000 deaths attributed to CNS cancer globally. The geographical regions with higher incidence include east Asia (98,000 to 122,000), western Europe (37,000 to 54,000), and south Asia (29,000 to 37,000) In 2021, it was estimated that more than 84,000 people were diagnosed with a primary brain tumor (including gliomas) in the United States of America (USA) [13].

The survival rate at 5 years for all malignant gliomas combined has increased due to development of new therapies: 36% in the period observed between 2009 and 2015 compared to 23% from 1975 to 1977. However, the specific 5-year survival rates vary across populations and glioma subtypes. Glioblastoma (aka astrocytoma grade 4), however, remains one of the most aggressive forms of cancer, with an average survival of about 12-15 months after resection, radiotherapy, and chemotherapy and a 5-year relative survival rate of ~ 5% [14].

On the platform of the Nation Brain Tumor Registry of China (NBTRC), an annual average of 12,768 cases of brain tumor had been registered during 2019–2020, which was roughly 10 times the number of cases reported in the previous decade [15].

In a prospective study conducted at the Oncology and Neurosurgery department of Bangabandhu Sheikh Mujib Medical University from July 2006 to June 2007, it was found that overall clinical experiences indicate that its incidence is not low even though there is no epidemiological and statistical data supporting the cases of brain tumors in Bangladesh [16].

The objective of our review work has been done to investigate brain tumor symptoms, risk factors, diagnosis, treatment, and rehabilitation after treatment for both adults and pediatrics.

Toward the end of our review work, facility for brain tumors in Bangladesh in terms of diagnosis, treatment, and rehabilitation has also been discussed. Various work conducted previously on this platform, has not been done comprehensively. Therefore, there is a need to write comprehensive review on the knowledge on symptoms, risk factors, diagnosis, treatment, early treatment and post treatment along with the available tools and facilities in a developing country like Bangladesh.

Chapter 2

Background

2.1 The Nervous System

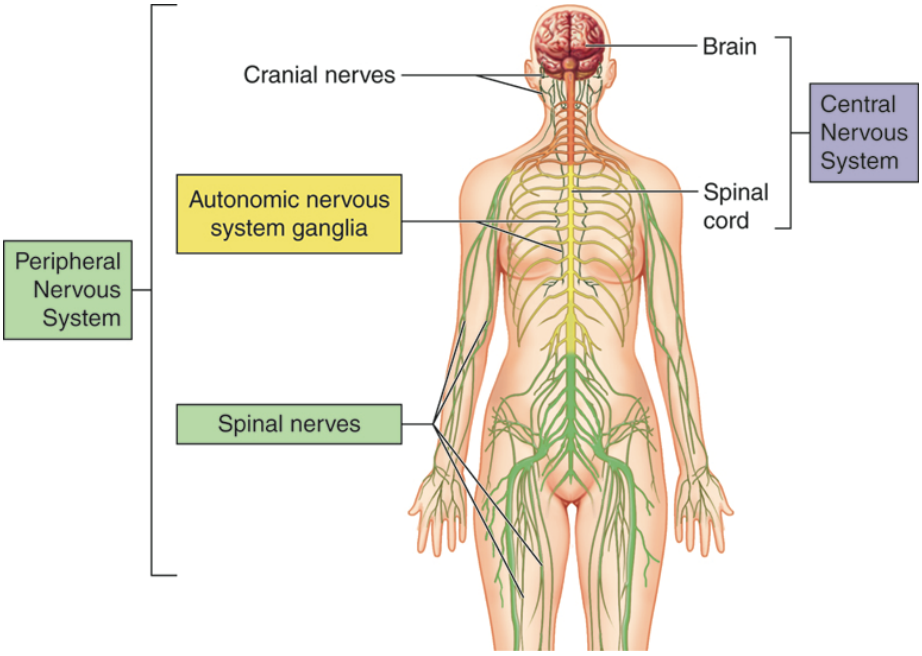

Figure (1): The two main components of the nervous system [17].

Neuroscience, neurobiology, and neurology- even though having different definitions, all fall under the same category of natural sciences. It contains vital information about biology and specific information about the nervous system [18]. The nervous system refers to a group of structured cells specialized in relaying electrochemical stimuli from sensory receptors to the specific reaction sites [19].

Decision making, communication throughout the body and functioning with other systems to conduct critical functions are the main roles of the nervous system. Various structures and divisions work together in the nervous system to produce behaviours and bring about a result which is specific to each human being [20].

To get tasks done, the nervous system connects its different parts and creates a team where they require help from each other. The two major components within the nervous system are the central nervous system and the peripheral nervous system [20].

Human with their highly developed brain and its unique ability of cognitive capacities for understanding, imaging, language, problem solving, and introspection are the set apart factor from rest of the creatures [21].

2.2 Components of the Nervous System

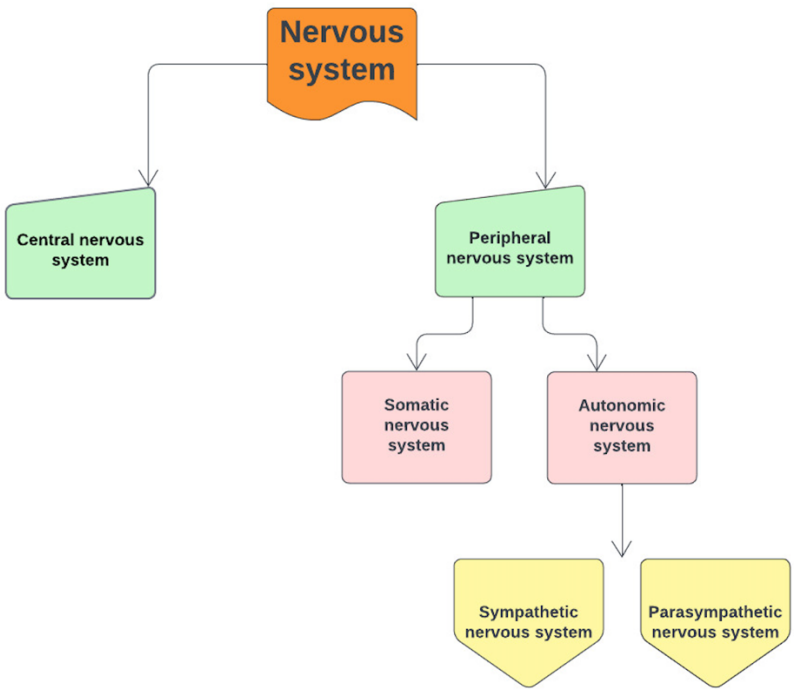

Figure (2): The components and sub-components of the Nervous system

2.2.1 The Central Nervous System (CNS)

The initial development of the central nervous system develops as a hollow tube and maintains this basic shape even after it is fully developed. The developmental stages involve the hollow

tube elongation, formation of pockets and folds and thickening of the tissue until the brain reaches the final form [22].

CNS is one of the two parts of the nervous system of the human body which is made up of the brain and the spinal cord. It is the body's processing center. The spinal cord is an extension with peripheral nerves connected to it which helps carrying messages to and from the brain [23]. Motor information are sent to the autonomic and somatic systems from the brain by the CNS. Bodily functions like speech, muscle movements, organ functions etc are then controlled by the brain [24].

Basic units called neurons, arranged in networks that carry electrical and chemical messages to and from the brain, make up the nervous system [25].

2.2.2 The Peripheral Nervous System (PNS)

The other component of the nervous system which plays a key role in transmitting vital information from various areas of the body back to the brain s well as from the brain to various parts of the body is the Peripheral Nervous System (PNS). The PNS includes everything except the brain and the spinal cord. Peripheral nerves, cranial nerves, and autonomic structures are part of the PNS [26].

PNS consist of two subsystems which are the autonomic and somatic nervous systems [27].

- **Autonomic**: processes that the brain runs automatically and unconsciously without us thinking much about them.
- **Somatic**: functions that are carried out consciously and by us having to think about it.

The PNS uses these two subsystems to do its three main jobs: [28]

- **Senses**: PNS gets information from the world around us through the somatic nervous system.
- **Movement**: Command signals are delivered to all the body muscles through the peripheral nerves that we consciously control. This is also done by the somatic nervous system.
- **Unconscious processes**: This depends on the autonomic nervous system, processes that run on the body without us much thinking about it. Examples of this include heartbeat and blood pressure.

The autonomic nervous system is further divided into two parts: sympathetic and parasympathetic divisions. The sympathetic division controls the 'fight or flight' responses meaning they prepare the body for energetic physical exercises. Parasympathetic system regulates the 'rest and digest' functions meaning they are responsible for energy conservation and maintaining vital body processes, especially when the body is at rest [29].

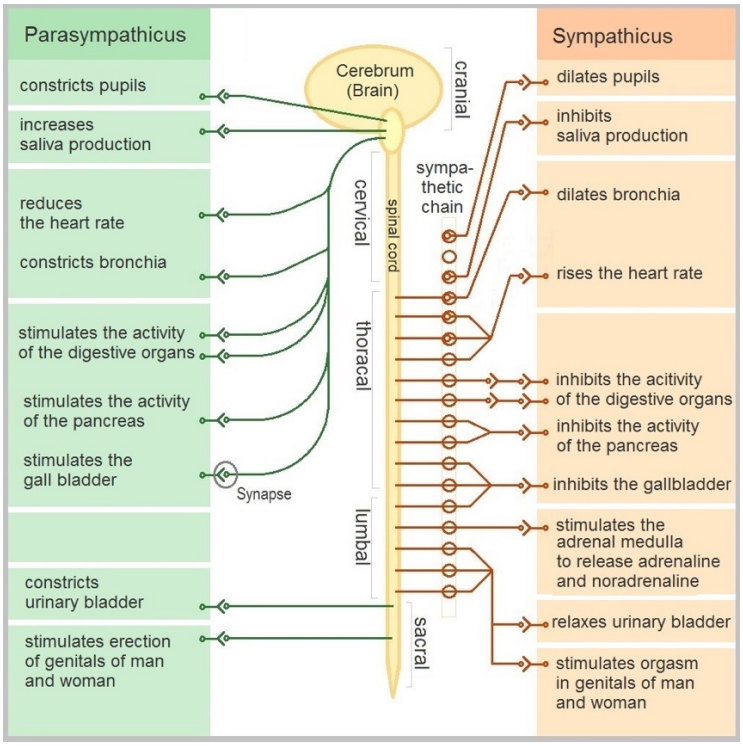

Figure (3): Few examples of the functions carried out by sympathetic and parasympathetic nervous system [30]

2.3 The Brain and It's Anatomy

2.3.1 Overview

The human brain is an elaborate collection of billions of cells operating together to process stimuli and observe needs to help direct behavior. The brain begins to develop at the most rostral extension of the neural tube from where it turns and twists while it expands within the restrains of the cranium (skull). The expansion of the brain is relatively disproportionate compared to the spinal cord growth which is the very rear extension of the central nervous system [31].

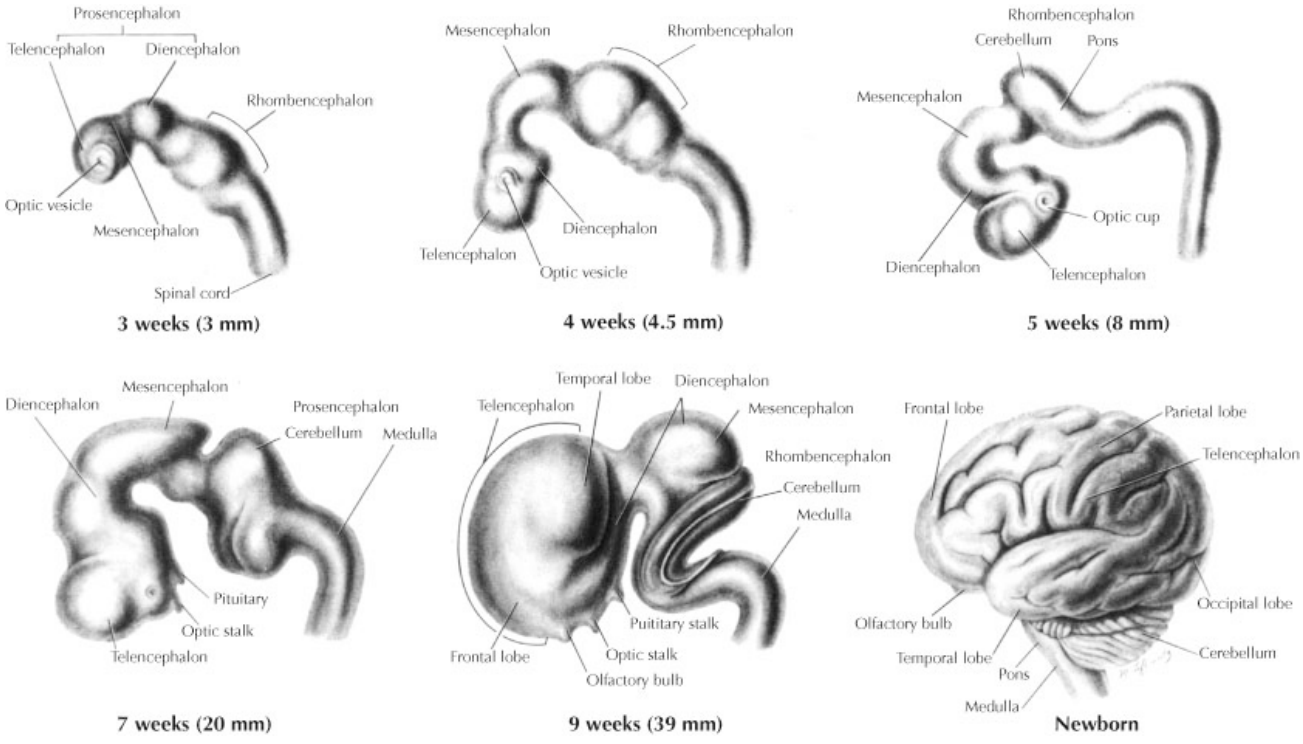

Figure (4): The development of the human brain, showing its major subdivisions. [31]

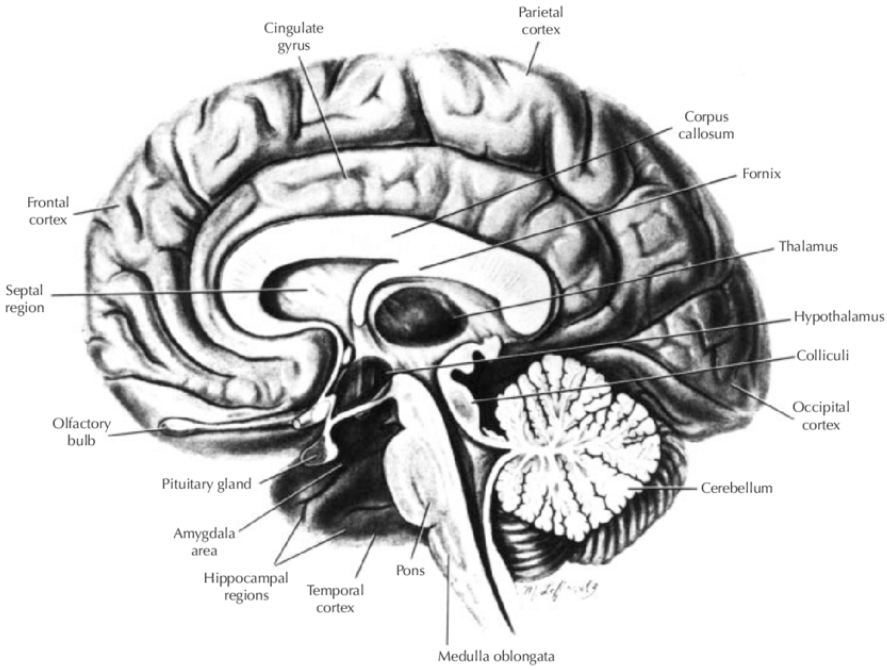

Figure (5): The location of the four lobes and other major brain structures of the adult brain [31].

2.3.2 The Brain & It's Parts

The three main parts of the brain are cerebrum, cerebellum, and brainstem. Figure 5 shows the basic anatomy of the brain and its major parts [8].

Cerebrum being the largest part of the brain composed of the right and the left hemispheres. The functions it performs include touch, hearing, seeing, speech, reasoning, emotions, learning, memory, and fine control of movement etc.

Cerebellum is located just under the cerebrum which coordinates muscular movements, helps maintain posture and balance.

Brainstem connects the cerebrum and cerebellum to the spinal cord. It acts as the relay center and helps in performing automatic functions like breathing, heart rate, body temperature, body clock, digestion, swallowing etc.

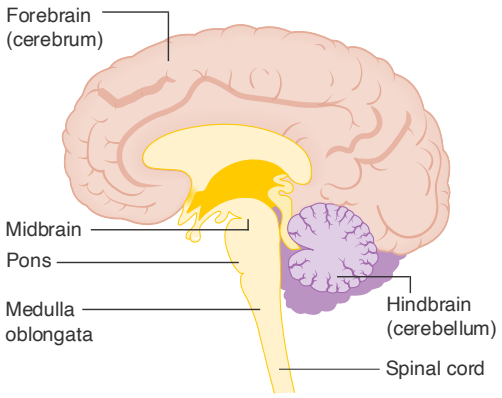

Figure (6): Gross anatomy of the human brain and its major constituent parts [32].

The brain consists of the brain stem and the cerebral hemispheres.

The brain stem is divided into 3 segments: hind-brain, mid-brain, and diencephalon or the 'between-brain'.

Hindbrain it is an extension of the spinal cord. They contain the neural networks that make up the control centers of crucial functions like breathing and blood pressure. Cerebellum plays an important role of control and timing of movements and arise from the roof of the hindbrain [33].

Mid-brain contains groups of neurons, each of which use a specific type of chemical messenger and ventures up to the cerebral hemispheres. They control the neural activity in the upper centers of the brain and maintains functions like sleep, attention, and focus [34].

The diencephalon is separated into two parts:

1. the thalamus- they relay impulses to the cerebral cortex from all from all the sensory systems, thus sending messages back to the thalamus. This back and forward connectivity of the messages in the brain proves that information travel is not one way.

2. the hypothalamus controls basic and important functions like eating and drinking for instance, regulation of hormones released involved for sexual purposes are also maintained.

The cerebral hemispheres make up the grey matter of the brain's cerebral cortex. The cortical tissue is divided into various areas each having discrete functions. Functions of areas such as visual, auditory, and olfactory and sensory areas etc. [33]. They consist of a core, the basal ganglia, and an extensive thin sheet of neurons.

2.3.3 Deeper structures within the brain

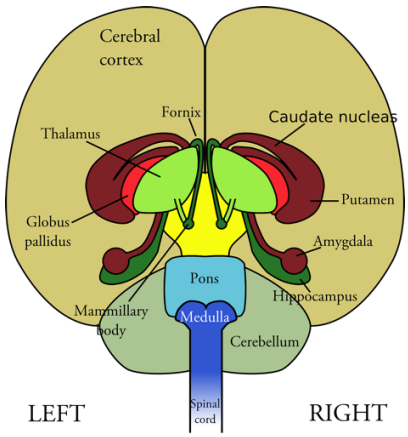

Figure (7): Deeper structures within the brain [35].

Deeper structures on the brain and their functions, referring to figure (7) above: [36]

- Hypothalamus is the main control of the autonomic system as it controls behaviors like as hunger, thirst, sleep, and sexual response. Regulation of body temperature, blood pressure, emotions, and secretion of hormones is also taken care of by the hypothalamus.
- Pituitary gland controls the endocrine glands which secretes hormones for sexual development, promotes bone and muscle growth and responds to stress. It lies in a small pocket of bone at the skull base from where the pituitary stalk connects the gland to the hypothalamus.

- Pineal gland aids in regulation of the bodily clock and secretes melatonin as well as help in sexual development. It is located behind the third ventricle.
- Thalamus is the relay station for all incoming and outgoing information to the cortex. Roles include pain sensation, focus, cautiousness, and memory.
- Basal ganglia are nuclei that work together with the cerebellum to manage motion like movement of fingertips.
- Limbic system behaves as the is the core of our emotions, learning, and memory. Included in this scheme are the hypothalamus, amygdala (emotional reactions) and hippocampus (memory).

2.3.4 Lobes of the brain

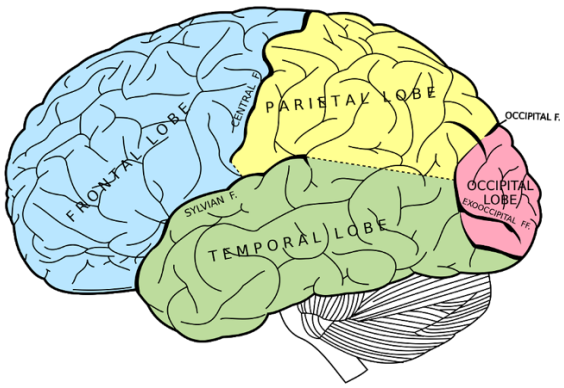

Figure (8): Lobes of the brain [37].

The cerebrum is divided into two halves: the left hemisphere and the right hemisphere. Corpus callosum is a bundle of fibers that join the two hemispheres to each other. They aid in transmission of messages from each side. Interestingly, each of the hemisphere regulates the opposite side of the body. For example, the left leg or arm may become paralyzed if the stroke occurs on the right side of the body.

More specifically, the left hemisphere is more dominant which controls speech, comprehension, arithmetic, and writing whereas the right hemisphere controls creativity, spatial ability, artistic, and musical skills [38].

Furthermore, cerebrum is divided into 4 lobes: Frontal, Temporal, Parietal and Occipital [8].

- **Frontal lobe:** This is the largest lobe of the brain located at the front of the head.
- **Parietal lobe:** The middle part of the brain
- **Occipital lobe:** Lobe at the back part of the brain
- **Temporal lobe:** Lobes at the side of the brain

Table (1): Lobes of the brain and their respective functions [8].

Lobes	Frontal	Temporal	Parietal	Occipital
Functions	Personality Behavior Emotion Judgement Planning Speech Movement	Understanding language Memory Hearing Organization	Interprets language. Sense of pain, touch, temperature Interprets signals from vision, hearing. Spatial and visual perception	Interprets vision like color, light and movement

2.3.5 Brain Coverings: Meninges

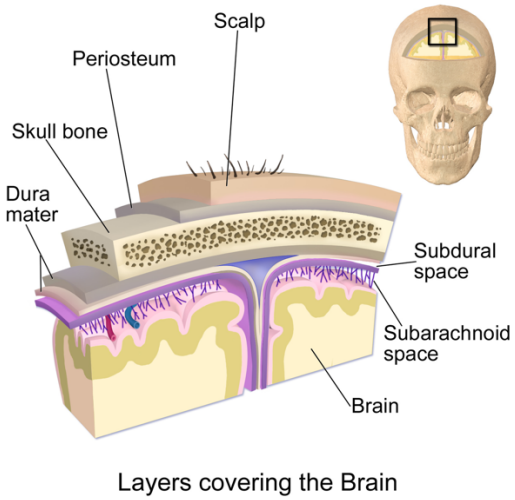

Figure (9): A schematic diagram of the meninges covering the brain and the spinal cord [39].

Referring to figure (9) above, three layers of protective covering called meninges surround the brain and the spinal cord called the dura mater, pia mater and arachnoid mater [40].

- The dura mater is the thick and tough outermost layer. Periosteal and meningeal layers are also included in this layer which covers the inner dome of the skull and the layer below that. The available gaps between the layer's aids in blood supply of veins and arteries to the brain.
- The arachnoid mater does not contain any nerves or blood vessels as they are a thin and spider web-like layer of connective tissues. The cerebrospinal fluid, or CSF which cushions the whole central nervous system (brain and spinal cord) and recurrently circulates around the CNS to help impurities to get removed.
- The pia mater hugs the brain surface being a thin layer, it is rich in veins and articles.

2.3.6 Blood Supply to the Brain

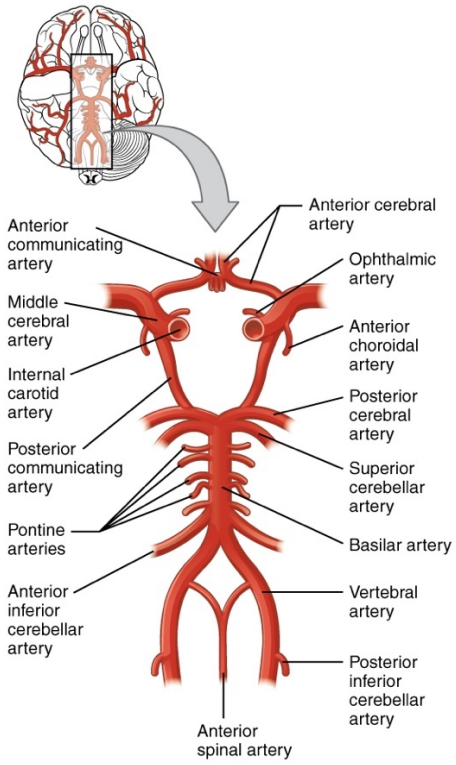

Figure (10): Nerves supplying blood to the brain [41]

The nerves that supply the cerebrum with blood are the paired vertebral and internal carotid arteries. They start in the neck and go all the way up to the cranium. The anastomotic circle known as the Circle of Willis is formed by the terminal branches of these arteries within the cranial vault. Majority of the cerebrum is supplied by branches that grow out of this circle [42]. Different pieces of the CNS, like the pons and spinal string, are provided by more modest branches from the vertebral supply routes.

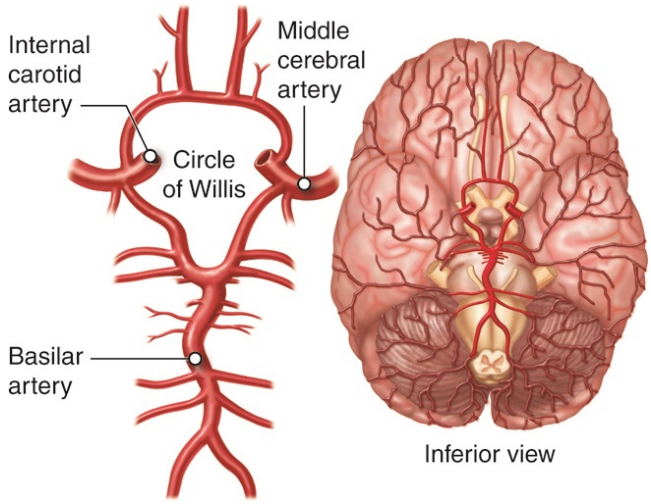

Figure (11): Formation of the Circle of Willis [43].

The internal carotid veins (ICA) start at the bifurcation of the left and right normal carotid conduits, at the level of the fourth cervical vertebrae (C4). They travel superiorly within the carotid sheath and enter the brain through the temporal bone's carotid canal. They supply no branches to the face or neck. Once in the cranial cavity, the interior carotids go anteriorly through the cavernous sinus, lateral portions of cerebrum are supplied with blood as the internal carotids continue as the middle cerebral artery [44].

2.4 Brain basics: Neuron anatomy

2.4.1 Neurons

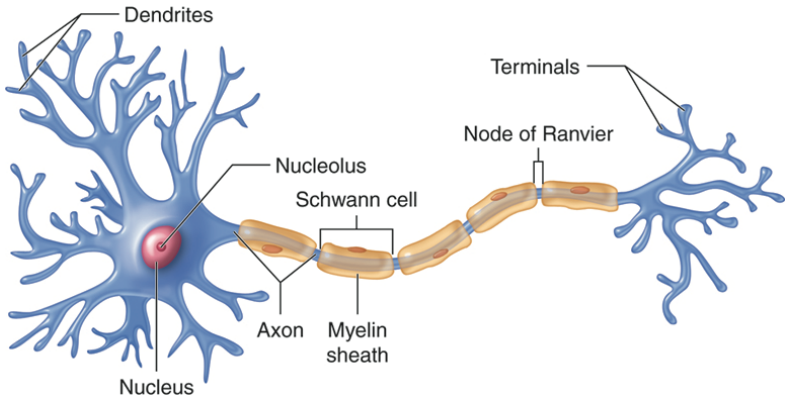

Figure (12): Structure of a neuron [45].

Nerve cells called neurons are partly what the spinal cord and brain are made of. Neurons refer to the basic functional cell of the nervous system that transmits impulses. A neuron functions to communicate [25].

With reference to the figure (12) above, the structure of a neuron consists of the following: [46]

- Dendrite- Receives stimulus and carries the impulses toward the cell body.
- Cell Body- Contains nucleus and most of the cytoplasm.
- Axon- Fiber which transports impulses away from the cell body.
- Schwann Cells- Myelin/fat layer producing cells in the Peripheral nervous system (PNS)
- Myelin Sheath- Dense layer of lipid which keeps axon insulated- gives the grey shade to the axon.
- Node of Ranvier- the gaps/nodes on the myelin sheath.

2.4.2 Synapsis

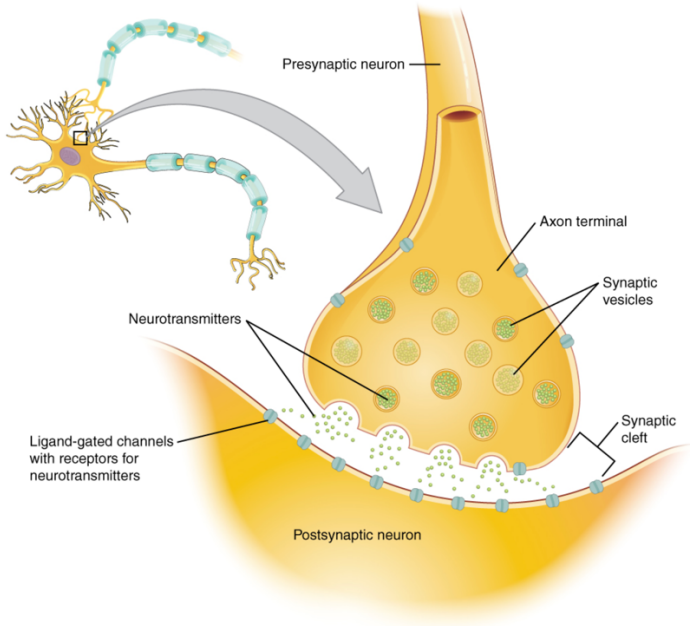

Figure (13): The basis of a synapse [47].

The figure (13) above describes the basis of a synapse. Referring to the image, the axon of neuron 1 communicates at the synaptic cleft (gap between the neurons) with the dendrite of neuron 2 to receive incoming synaptic information. Whereas in the brain, the myelin-coated axons are on the inside, while the axon-dendrite network is on the outside. This happens in the opposite way for spinal cord [25].

Myelin is an insulating layer around the nerve fibers that allows electrical impulses to transmit efficiently. It appears to be white as it is made up of compounds like proteins and phospholipids. The spinal cord and brain regions are made up of gray and white matter- white matter refer to the myelinated regions. The white matter which surrounds the spinal cord help transmit and carry information up to the brain via sensory tracts and from the brain to the spinal cord using motor tracts. The gray matter comprises of neuron cell bodies and glial cells which

play a crucial role in effective neural communication. Neurons synapses in the grey matter- they pass electrical or chemical signals from one to another [25].

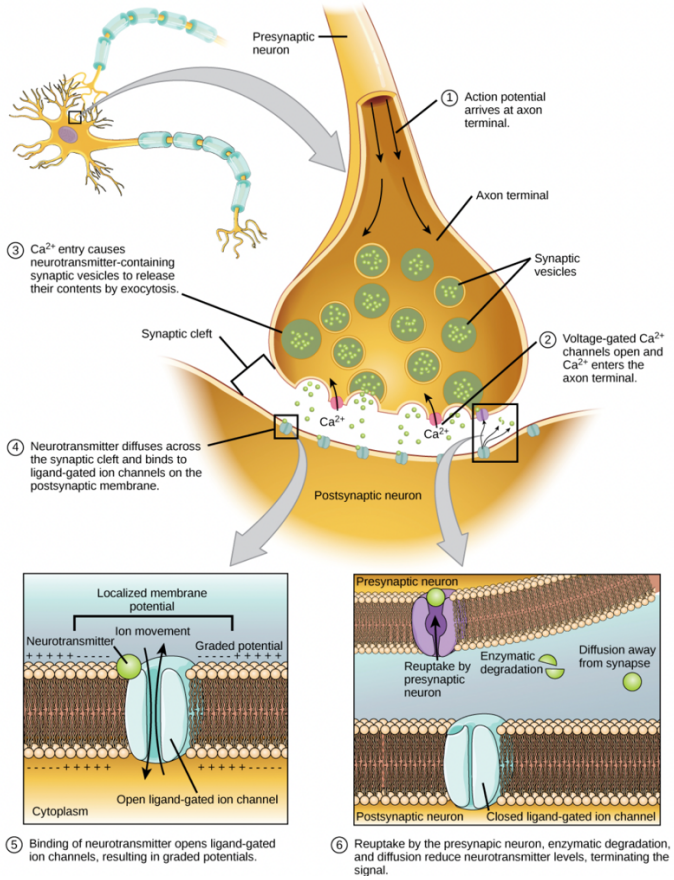

Fig (14): Occurrence of an action potential in the postsynaptic neuron [48].

Action potentials circulate a signal along the axonal length [49]. Largely, an action potential is referred to a rapid sequence of changes in voltage across a membrane. Membrane voltage or membrane potential is always determined by the relative ratio of extracellular to intracellular ions and the permeability of each ion. In neurons, depolarization, a rapid increase in potential, is an all-or-nothing event triggered by the opening of sodium ion channels in the plasma membrane. The subsequent return to the resting potential, repolarization, is mediated by the opening of potassium ion channels. To restore the proper ion balance, an ATP-driven pump

(Na/K-ATPase) induces the movement of sodium ions out of the cell and potassium ions into the cell [50].

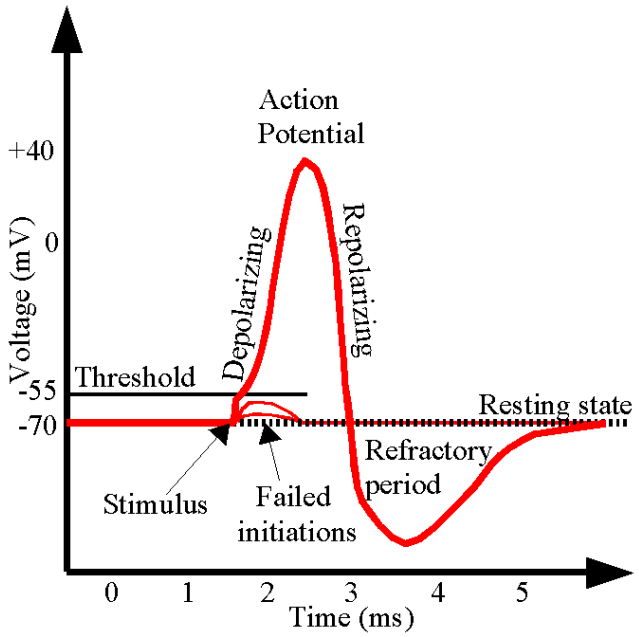

Fig (15): Transmission of an Action Potential [51].

The voltage across the member determines the opening and the closing of the voltage gated channels. These are the sodium and potassium voltage gated channels in the nerve cell. A signal at a sensory receptor or dendrite triggers the sodium channels to open which lets sodium enter the neuron. The influx of sodium ions (Na^+ in) leads to the membrane potential being positive. Threshold potential is a sufficient charge achieved in membrane [52]. Adjacent voltage-gated sodium channels open when the threshold potential is achieved, concluding in a state of depolarization that spreads down to the axon. The state of depolarization is the action potential. This charge change causes the potassium gates to open increasing an influx of potassium ions to exit the neuron continuously. The outflow of potassium ions out of the neuron causes the membrane potential to be negative again- state of repolarization. The initial distribution of ions (Na^+ out, K^+ in) must be re-established by the Na^+/K^+ pump before neuron can fire again. Now

is the refractory period where there is incapability to circulate another action potential which guarantees nerve impulses to travel in just one direction [53].

2.5 Cranial Nerves

The cranial nerves originate from a miscellaneous group of nuclei and ganglia and innervate mostly the skin and muscles of the shoulder, back of the head, and neck. These nerves are vital for numerous communications skills of humans like facial expression, language, sight, smell, taste, and hearing [54]. These nerves send electric signals between the brain and between parts of the neck, head, and torso [55].

Two of the cranial nerve pairs are devised in the largest portion of the brain, the cerebrum. The two pairs of cranial nerves include:

- **Olfactory nerves:** controls sense of smell.
- **Optic nerves:** controls the ability to see (vision)

The other 10 pairs of cranial nerves start in the lowest part of the brain, the brainstem, which connects the brain to the spinal cord.

These cranial nerves have functions in controlling various sensations and motor skills. Sensory nerves aid in the feelings of touch, hear, smell, taste, and smell whereas motor nerves control the muscles of the face [55].

Human beings have 12 cranial nerve pairs in total. Each of these nerve pair splits to attend the two sides of the brain and body. The nerves (one at each side of the body) are as follows: [56]

Table (2): 12 cranial nerve names and what they control.

Nerves	Functions
1. Olfactory	Sense of smell
2. Optic	Vision
3. Oculomotor	Muscle movements of the eyes (extraocular muscles)
4. Trochlear	Eye movement: roll it backwards, forwards and sideways
5. Trigeminal	Sensations in face, cheeks, taste and jaw movements
6. Abducens	Control eye movements
7. Facial	Controls facial expression; taste sensations and sensations of external ear
8. Auditory/ vestibular	Sense of hearing; sense of balance
9. Glossopharyngeal	Sensation of taste and ability to swallow
10. Vagus	Aids in digestion and heart rate; movement of throat
11. Accessory (or spinal accessory)	Muscle movements of the shoulder and neck
12. Hypoglossal	Tongue movements

2.6 Neurotransmitters

Neurotransmitters are chemical messengers that carry signals from neurons through synapses to target cells, they are necessary for the speedy communication in synapse [57]. They aid in the amplification, transmission and conversion of signals and information throughout the nervous system. Recently it is being studied that disturbances in the neurotransmitters could be correlated with neurological and degenerative diseases [58].

These chemical messengers are produced in the presynaptic neuron and released under physiological conditions. Here, they are localized into vesicles and released from the synaptic

cleft by degradation or uptake. Receptors are present on the post synaptic neuron where they bind and bring about a biological response [57]. This is how neurotransmitters convey their messages- by attaching to the target cells specific receptors by travelling between cells. Each neurotransmitter is specific to a special receptor. For instance, dopamine molecules will only be able to attach to dopamine receptors. An action is triggered after the transmitter is attached to the receptor. After the message is delivered, they are broken down and recycled by the body [59].

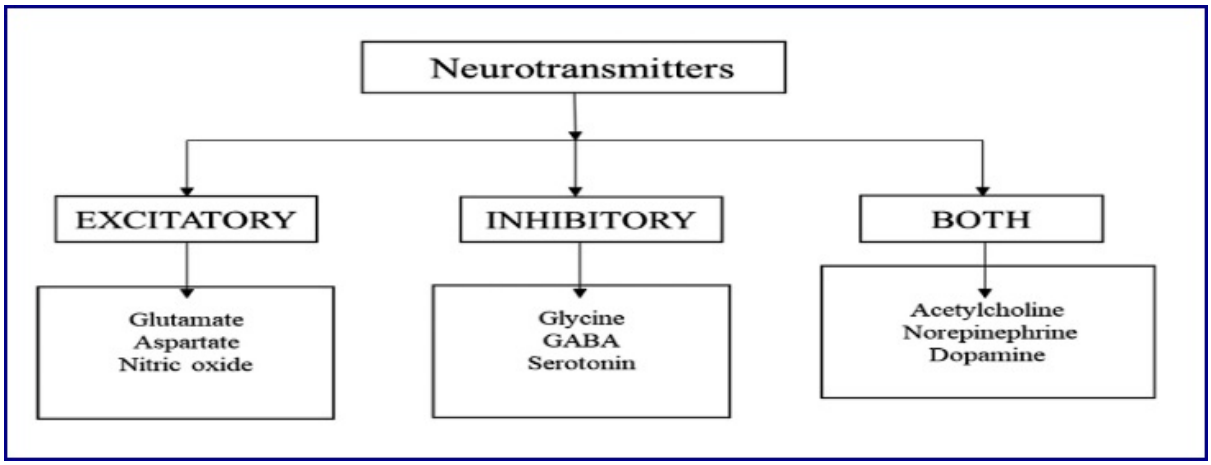

Figure (16) Neurotransmitters and their types and divisions [60].

There are 7 amino acids that are major neurotransmitters in the body, each falling under different categories as shown in figure above [58]

1. Glutamate:

Being a common dietary amino acid, this chemical acts as an excitatory neurotransmitter. They stimulate neurons to fire commands in the CNS. High levels of glutamate can be tricky for the brain as the can over-excite cells where the neurons find it tough to bring the energy back to normal level. Glutamate is responsible for neuroplasticity, as these amino acids are needed to construct pathways between neurons and strengthen memory and the ability to learn.

2. GABA (γ-aminobutyric acid)

GABA, being exactly opposite to glutamate is the main inhibitory neurotransmitter. It makes the central nervous system inactive and blocks few signals from the brain. It helps the brain to relax and has a calming effect that slows a person down by decreasing the heart rate and stimulates sleep. GABA helps in lowering stress levels.

3. Dopamine

Dopamine has a big role to play in the brain's reward system. Dopamine perks up the brain and produces feelings of joy and pleasure when a goal is achieved, or task is completed.

There are certain drugs that incite the brain to yield excess of dopamine which creates temporary sensations of pleasure or a high. But here is when it can get tricky as it is a challenge to come down from an abundance of dopamine. Feelings of depression, tiredness, low motivation in favorite activities might follow.

The pros of dopamine are:

- It encourages alertness.
- Helps pancreas release the proper amount of insulin after meals.
- Syncs brain and body to generate voluntary movement.

4. Adrenaline (Epinephrine)

Adrenal glands, located above the kidneys, produce adrenaline This neurotransmitter is accountable for body's fight or flight response. They travel throughout the CNS to increase heart rate to brin oxygen to the muscles rapidly. It also behaves as a defense mechanism against stress in the body. Adrenaline improves decision making as well.

5. Serotonin

This chemical messenger is present in the digestive tract and promotes feelings of satisfaction after eating as well as keeping check of appetite. It kicks in right when something does not feel right in the stomach, for example, after eating rotten or spoilt food. The potentially toxic food triggers serotonin which creates sensations of nauseousness and help bowel dispose the food off quickly.

6. Oxytocin

Oxytocin neurotransmitters are made in the hypothalamus and released all over the body via the pituitary gland. They are helpful in physical and social health. They help in:

- Uterus wall contraction while childbirth
- Nurtures the unique bond between mother and a child
- Stimulates release of breast milk from mammary glands
- For men, oxytocin stimulate feeling of trust and loyalty.

7. Acetylcholine

Directly affecting the muscles, this neurotransmitter works at where the nervous system meets the muscles. When acetylcholine is released from neurons, receptor proteins on muscle fibers take it up. The presence of acetylcholine, in turn, triggers action potentials or commands in muscle fibers instead of sending signals to brain cells, acetylcholine causes muscles to contract. They take care of voluntary movements like heartbeat or peristalsis contractions.

Chapter 3

Brain Tumor

3.1 What is a brain tumor:

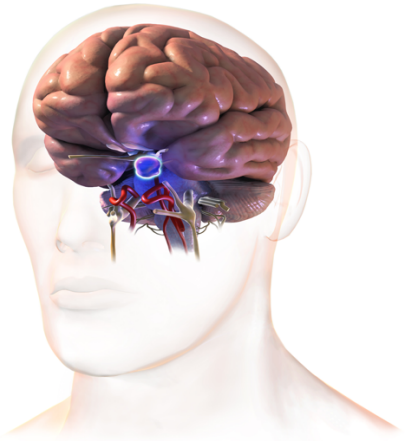

Figure (17): Formation of brain tumor in brain cells [61].

Any tumor is referred to as an uncontrolled growth of cells which forms an abnormal mass of tissue. This occurs when cells grow and divide more than it is required, or they still persist in the body when they should not [62].

Brain tumor, which is also known as intracranial tumor, is a mass or growth of abnormal cells in the brain. These cells grow and multiply uncontrollably. Brain tumors can be cancerous (malignant) or non-cancerous (benign). These tumors can begin in the brain (primary brain tumors), or cancer can begin in other parts of your body and spread to the brain as secondary (metastatic) brain tumors. Many kinds of brain tumors exist [9]. How quickly a brain tumor grows can vary greatly. The growth rate as well as the location of a brain tumor determines

how it will affect the function of the nervous system. Brain tumor treatment options depend on the type of brain tumor- its size and location [63].

A brain tumor can form in the brain cells as shown below in the diagram figure (19), or it can originate somewhere else in the body most commonly lungs, breast, kidney, and colon etc. and spread to the brain as secondary tumors as mentioned above [64]. Pressure and other changes in the surrounding brain tissues, nerves and vessels increase with the growth of the tumor. This results in the occurrence of the signs and symptoms as common as headaches, nausea, and body balance issues [9].

There are over 120 different types of brain tumors, lesions, and cysts, depending on where they occur and what type of cell they are. Classification of brain tumors can be done at a molecular level depending on their microscopic features and characteristics of their tissues. They are graded for comparison and classification purposes based on the severity within a certain type [65].

In general, tumors may be CNS WHO grade 1, which is the least aggressive, up to CNS WHO grade 4, which is the most aggressive: [64]

- **Grade 1.** The cells appear to be normal with slow growth. Expected to survive long term.
- **Grade 2.** The cells appear to look vaguely abnormal with slow growth. Extending to a life-threatening grade, tumor might spread to neighboring tissues.
- **Grade 3.** The cells look abnormal with fast growth into neighboring brain tissues, fall into category of tumors that come back.
- **Grade 4.** The cells look most abnormal, grows and spreads rapidly.

Most primary brain tumors fall under the WHO classification scheme (grade) of tumor of neuroepithelial tissue. More than 80% of primary brain neoplasms are malignant gliomas being the most common brain tumor [66].

3.2 Common types of brain tumors

Brain and spinal cord tumors could be regarded as a heterogeneous group of diseases containing approximately 100 various kinds of tumors. Brain tumors are categorized according to their similarity to the normal cellular composition of the brain. The most common types of brain tumors are Gliomas, Meningiomas, Metastases, Embryonal tumors and ependymomas.

- **Gliomas**- Gliomas, which appear from glial cells, are found to be the largest and the most common variant of all primary central nervous system neoplasms. In the United States, 6 out of 100,000 people are diagnosed with glioma each year [67]. These tumors have the capacity to be low grade or high grade, as graded by the World Health Organization (WHO), depending on their potential aggressiveness. They are highly diffuse and invasive in nature which affects surrounding brain tissues [68]. Astrocytoma (subtype 1) and oligodendroglioma (subtype 2) are its two subtypes.

  Astrocytoma (subtype 1 of glioma)

  Astrocytoma's form in astrocytes, a type of star-shaped glial cell in the cerebrum [69]. This is the most common glioma, affecting the brain and occasionally, the spinal cord. They account for 60% of brain tumors and a common cause of mortality in both young and old [70]. There are many types of astrocytoma's having different grades by the World Health Organization tumor grading system. They are:

  Anaplastic astrocytoma: grade III (sometimes I/II): rare but aggressive

  Pilocytic astrocytoma: grade I: most benign

Subependymal giant cell astrocytoma: grade I: usually associated with tuberous sclerosis.

Low-grade astrocytoma: grade II: slow growers, invades neighboring tissues.

Glioblastoma (which often progresses to grade IV) is very aggressive.

Symptoms of astrocytoma commonly include headaches due to increased intracranial pressure, seizures, memory loss, behavioral changes, head tilts, incoordination, stiff neck, nausea, vomiting, nervousness, and visual disturbances. Astrocytoma's can be treated with a combination of surgery, radiation therapy, observation, follow-up imaging, chemotherapy, and ventricular shunt. Each tumor grade requires precise treatment based on individual characteristics [71].

The typical survival ranges for the different types of astrocytoma's are: [71]

- Pilocytic astrocytoma (grade I): >10 years
- Low-grade diffuse astrocytoma (grade II): > 5 years
- Anaplastic astrocytoma (grade III): ~ 2 to 5 years
- Glioblastoma (grade IV): ~1 year

Low-grade astrocytoma has a ratio of 1.18:1 male: female ratio

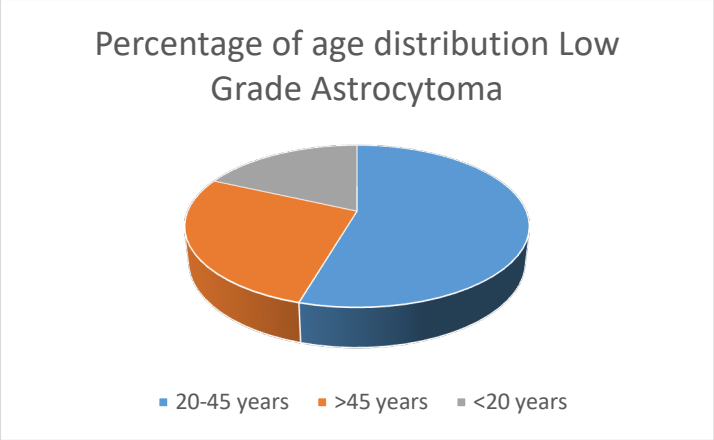

Figure (18): Shows the distribution of age of low-grade Astrocytoma [71].

As shown in the fig (18) above, these tumors occur the most (60%) in adults ageing from 20-45 years of age, occurs in mid-aged adults (30%) who are over 45 years of age and occurs lowest in young adults (20%) who are under 20 years of age [71].

Oligodendroglioma (subtype 2 of glioma)

These tumors are the other subtype of gliomas mentioned above. Arising from oligodendrocytes, cells that makeup supporting glial tissues of the brain cell, are found throughout the cerebral hemispheres but most commonly in the frontal and temporal lobes [72].

Oligodendrogliomas are divided into two grades based on their characteristics. Grade II oligodendrogliomas are low-grade tumors. This means that tumor cells grow slowly and invade nearby normal tissue. It forms years before diagnosis because it is often asymptomatic. Grade III oligodendrogliomas are malignant. This means that these are fast growing tumors. They are called undifferentiated oligodendrogliomas [73]. They are generally soft greyish-pink tumors that often contain calcifications (mineral deposits), hemorrhages or cysts.

Common symptoms include seizures, headaches, and personality changes. Other symptoms depend on the size and location of the tumor [74]. They typically occur in middle-aged adults or children as partially calcified cortical or subcortical masses [75].

- **Meningiomas**

They are the one of the most common primary central nervous system tumors. They make up approximately one-third of all intracranial tumors [76]. Arising from the cells that line the inside of the brain(meninges), they tend to be slow growers and are likely to grow on the surface of the brain [77].

Although they have a reputation for being a benign condition, these dural-based tumors can result in morbidity and exist with a multiplicity of nonspecific, site-dependent manifestations [78]. They are usually removed with surgery, but some meningiomas behave more aggressively and may require additional treatment, usually radiation [79].

Meningiomas have 15 subtypes which are graded with grade I to grade III on by the World Health Organization based on histologic criteria. The pie chart below shoes the percentage of the meningiomas belonging to each of the grades according to WHO.

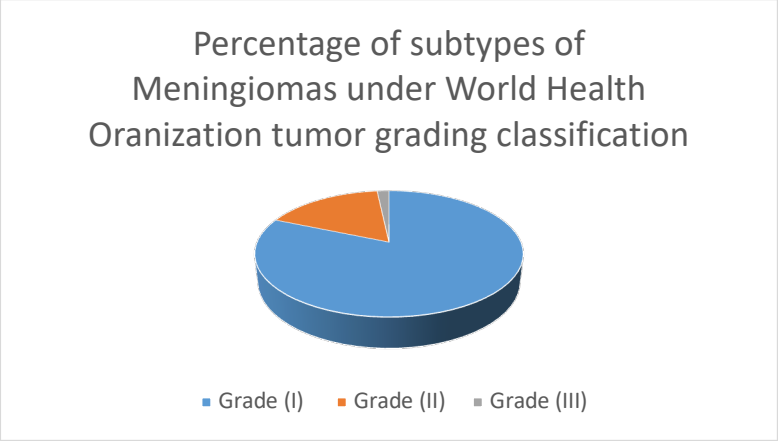

Figure (19): Pie chart showing the percentage of the subtypes of meningiomas under each grade by the tumor classification by World Health Organization (WHO) [79].

Symptoms of meningiomas might be very subtle and gradually start becoming more severe. Symptoms may include double vision or blurriness, tremendous headache in the morning, hearing loss, memory loss and loss of smell etc. [80].

- **Metastases**

  Formation of brain metastases (BM) occur when cancer cells spread from their original site in the brain. Any cancer can spread to the brain, but the types that usually cause brain metastasis are lung, breast, colon, kidney, and melanoma [81]. Brain metastases tend to cause deterioration of neurological function and adversely affect the patient's quality of life. Control of brain metastases is important following improved outcomes seen in cancer patients [82].

  They are the most common cause of all malignancies of the central nervous system being four times more frequent than the occurrence of primary tumors. Roughly, 20-40% of cancer patients develop BM during their clinical course. With each passing year, its incidence has been increasing because of the increase in the overall survival (OS) of cancer patients and the improvement of diagnostic tools for BM detection for instance magnetic resonance imaging (MRI) [83].

  As a metastatic brain tumor grows, it puts pressure on the proximate brain tissue and changes its function. This causes the very typical symptoms such as headaches, personality changes, memory loss, and seizures etc. [84].

- **Embryonal brain tumors**

  Embryonal tumors of the central nervous system are high-grade neoplasms that largely affect the pediatric population. These brain tumors arise from the left-over cells (germ cells) from the early stages of development from the womb. They are usually harmless but can also hold the risk of turning into cancer [85].

  There are different types of embryonic brain tumors. The most common form is medulloblastoma, which mainly affects children. Aggressive treatment such as chemotherapy and radiation are required. Extensive radiation may be required because these tumors tend to spread along the cerebrospinal fluid [86].

Medulloblastoma (subtype of embryonal brain tumor)

Medulloblastoma is the most common solid malignant brain tumor in children and adolescents. They account for nearly 20% of all childhood brain tumors. These tumors are highly undivided and rapid growers. Starting from the cerebellum, which is at the back part of the brain, they are high-grade tumors that spreads throughout the cerebrospinal fluid (CSF) in the brain [87]. Symptoms of medulloblastoma develop when the tumor grows or puts pressure on the brain. It can begin before the cancer is diagnosed and last months to years after treatment. Common symptoms of medulloblastoma include dizziness, double vision, poor coordination, headaches etc. [88].

The 3D column graph below shows the incidence of medulloblastoma in infants, children and adolescents. Children aged 4 to 9 years have the highest incidence at 44%, followed by adolescents (10 to 16 years) with 23% and infants/toddlers (0 to 3 years) with a small incidence of 12%. According to calculations, the incidence in children is 10 times higher than in adults. Men were 1.5 times more likely to have medulloblastoma than women. [89].

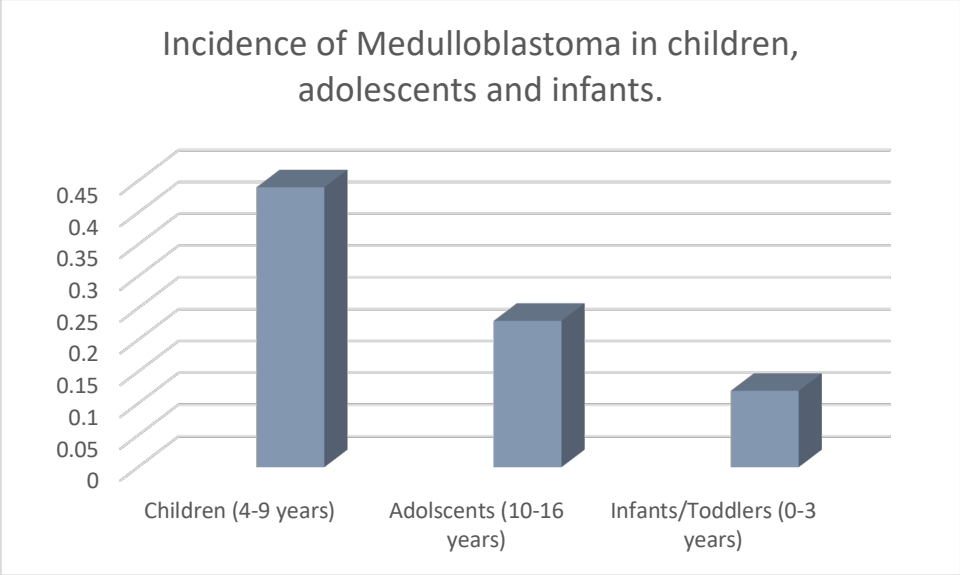

Figure (20): Column graph shows the incidence of medulloblastoma in children, adolescents, and infants [89].

- **Ependymomas**

  Ependymomas are glial cell tumors which forms in the brain or spinal cord [90]. These are solid tumors arising in the lining of the ventricular system and rarely outside the central nervous system or within brain parenchyma. They consist of genetically distinct subsets of tumors and affect children more frequently than adults [91]. According to the WHO tumor classification grading system, ependymomas are graded grade (II) and grade (III) [92].

  Because these tumors are solid, they can be completely removed surgically, but in some areas, this is not always possible and more aggressive treatment may be required. As ependymoma occurs in different CNS compartments, its clinical manifestations range from an acute onset of intracranial hypertension that causes nausea and vomiting to a more chronic and insidious clinical course [93].

3.3 Types of Benign Brain Tumors

Benign brain tumors are non-cancerous mass of cells that grows comparatively slowly in the brain. They manage to stay at a specific spot and not spread. If surgery is used to remove these tumors, they usually do not form back [94]. Nonetheless, if there is a failure to remove the tumor efficiently, a risk persists of it growing back. In this case, regular scans and treatment with radiotherapy could be helpful. There are many different types of benign brain tumors each affecting a different brain cell [95].

Below are listed down the most common brain tumors and the comparatively not-so common ones. [96] [97] [98].

Table (3): Types of benign brain tumors and their characteristics

No.	Type of tumor	Characteristic
1.	Chordomas	Benign (non-cancerous) Slow growers Common in 50–60-year aged people Rare tumors Common location: skull base and lower portion of spine Has capability to invade surrounding bone tissues and impose pressure on neural tissues
2.	Craniopharyngiomas	Benign Location being deep into the brain Critical to remove Frequently arise from pituitary gland tissues Patients require hormone replacement therapy.
3.	Gangliocytomas	Slow growers Common occur in young adults aged 10-30 years

4.	Meningiomas	Most common benign intracranial tumor 10-15% of all brain neoplasms Very small percentage of them are malignant. Originate from meninges.
5.	Pineocytomas	Benign lesions Arise from pineal cells which make melatonin Well-defined. Non-invasive- rarely spreads to other parts of the brain. Slow growers Occurs mainly in adults.
6.	Pituitary adenomas	Another common tumor intracranial tumor Most of them are benign, have malignant versions too. Slow growers Affect adults of 30-40 years of age
7.	Schwannomas	Benign PNS tumor, also have malignant version Arise along cells that provide electrical insulation- the nerve sheath. They displace the normal nerve cells Rare tumor
8.	Adenomas	Occurs in the epithelial tissue Can also grow in thyroid, pituitary or adrenal glands Non-invasive They can grow and exert pressure on surrounding structures
9.	Glomus Jugular	Grows in the temporal skull bone called jugular foramen Rare tumors Common in adults of 60-70 years of age
10.	Lipomas	They grow from fat cells. Benign intracranial tumor Locations: back, shoulder, arms, or neck

		Commonly they appear to be round and can be moved under the skin Rarely turns malignant Most common in mid aged adults of 40-60 years
11.	Nasopharyngeal Angiofibroma	Skull-based tumor Commonly diagnosed in adolescent boys Common tumor of the nasopharynx (space at the back of the nose connecting nose and mouth) Spreads to areas around the nose
12.	Choroid Plexus Tumor	Rare tumors found in choroid plexus which produces CSF (cerebrospinal fluid) with ventricles. Common in children of age 2, causes hydrocephalus (buildup of CSF) for them Causes skull enlargement and poses pressure on brain
13.	Neurofibroma	Painless benign tumors Develop in cranial nerves or spinal cord
14	Hemangioblastoma	Tumor of blood vessels that form in the brain Rarely, they occur in multiple sites where removal becomes tough
15.	Giant cell tumor	Consist of large cells as the name suggests. Rare bone tumors that could be found in skull bones Occur in patients of 20-40 years of age
16.	Osteoma	Benign bone tumors Develop in skull base or facial bones Slow growers Large osteomas could form on certain areas of the brain which cause problem in breathing, hearing or vision

3.4 Brain Tumors with Viable Grades (More Benign to Malignant)

Table (4): Types of brain tumors from more benign to malignant & their characteristics

No.	Types of benign to malignant brain tumor	Characteristics	References
1.	Gliomas	Common brain tumor Found in brain and spinal cord. Arise from glial cells. Growth pattern highly invasive Various types of gliomas exist	[99]
2.	Astrocytoma	Grade I/II Gliomas Slow growers Found in both children and adults Can be removed by surgery	[64],[71]
3.	Oligodendrogliomas	Arise from glial cells Occur in frontal lobe Low graded neoplasms Slow growers Good response to treatment	[74],[75]
4.	Glioblastomas	Common and aggressive neoplasm Grade IV brain tumors Arise from several neural stem-cell like properties. Occur in average age 64 and also childhood. First line treatment: chemotherapy	[100], [101]
5.	Ependymal tumors	Arise from the cells lining the ventricles Rare but malignant tumors Occur in both adults and in children	[102]

		Different types include: Sub ependymoma, Myxopapillary ependymoma and Ependymoma	
6.	Ependymoma	Glial cell tumors Have genetic mutations. Their behavior depends on their location in the nervous system	[103]
7	Hemangiopericytoma	Rare skull-based tumors Found in soft tissues. They can occur both as benign and malignant	[104]
8	Germ cell tumors	If germ cells accidentally enter the brain, they can become tumors. Can either be benign or malignant. They are localized in the pineal gland and suprasellar region of the brain. They are often diagnosed during puberty and occur more in boys than girls	[105]
9	Pineal Tumors	Occur in the pineal gland region. Located in deeper structures of the brain. Various types exist. Diagnosis includes a blood test or lumbar puncture to look for markers or surgery for a biopsy	[106]

3.5 Malignant Brain Tumors

Stated below are some points about each malignant brain tumor [107] [108]

Table (5) Types of malignant brain tumors and their characteristics

No.	Types of malignant brain tumor	Characteristics
1.	Chordomas	Rare form of bone cancer Found usually in the skull base or lower back. Has ability to invade surrounding bone and pose pressure on nearby nerve tissue. Slow growers Looks like benign but are invasive. Aggressive and progresses unpredictably.
2.	Chondrosarcoma	Malignant bone cancer affecting cartilage Develops commonly in patients of 50-70 years of age Tumor may begin in skull base or face bones. Aggressive in nature
3.	Astrocytomas	Common gliomas Develop from astrocytes which are small star shaped glial cells- part of supportive brain tissue. Can occur in any part of brain but most frequently in cerebrum. More prevalent in adults- mid aged men Develop near the skull base are more common in young people They are high grade for older people, low grade for younger ones

4.	Medulloblastoma	Common brain cancer in children of age 5-9 Rare in people over 30 Arises in cerebellum, located in skull base. Different kinds exist depending on exact mutations of the tumor cells
5.	Olfactory Neuroblastoma	Rare malignant tumor, develops in the nose Often start in the olfactory nerve- which transmits impulses related to smell from the nose to the brain
6.	Lymphoma	Tumor that forms the lymphatic system – a part in body's immune system Can spread to parts of the brain or body parts Biopsy recommended to figure out its type followed by Surgery, chemotherapy or radiation might be recommended for primary CNS lymphomas
7	Gliosarcoma	Tumors which are rare types of gliomas Ability to spread to other areas Aggressive growth Resistant to therapy
8	Rhabdomyosarcoma	Rare form of soft tissue cancer which forms on muscle Found in head, neck, and the skull base More likely to develop in children Inherited condition like neurofibromatosis type 1 (NF1) increases the risk of this cancer formation
9	Paranasal cancer sinus	Malignant skull base tumor Form in the tissue lining of the hollow spaces in the bone around the nose Found in maxillary sinuses (cheekbones under eyes) and ethmoid sinuses (beside upper nose)

10.	Atypical Teratoid/ Rhabdoid Tumor	Rare embryonal tumor of CNS Commonly affects children of age 6 or younger Fast growing Low survival rate

Chapter 4

Symptoms

Symptoms are referred as a physical or mental difficulty that a person experiences that may signify a disease or illness. Symptoms can only be identified and described by the affected person, such as fatigue, nausea, pain. A sign is something that other people can identify and measure such as fever, skin rash, or increased heart rate. Combining signs and symptoms can help explain a medical problem. People with brain tumors may not have any of the signs or symptoms described below. Alternatively, symptoms or signs may be caused by a medical condition other than a brain tumor [109].

Brain tumor symptoms may be common or specific. Common symptoms are caused by a tumor pressing against the brain or spinal cord. When a specific part of the brain do not function properly due to a tumor, certain symptoms are caused. Many people with brain tumors are diagnosed when they see a doctor after experiencing problems such as headaches or other changes. The signs and symptoms of a brain tumor vary greatly and depend on the brain tumor's size, location, and rate of growth [109].

The clinical presentation of brain tumors is confusing and varies greatly with tumor category, location, size, and growth rate as mentioned above. From an etiological point of view, the clinical features can be divided into increased intracranial pressure and increased local pressure, characteristic of natural tissue destruction. To date, headaches were found to be the most reported symptom in patients. Headache is categorized as a common medical condition and is a common ailment in nearly half of those affected. Headache is the first symptom in most cases. In addition to headaches and seizures, other symptoms include nausea and

vomiting, ataxia, visual disturbances, personality and behavioral changes, language disturbances, altered consciousness, sleep disturbances, drowsiness, fatigue, memory problems, partial tingling etc. [110].

4.1 Generalized physical symptoms

Headache

Headache is very common symptom of all patients for most illnesses, including those with brain tumors. Claims have also been made that there is a classic "brain tumor headache type". This special headache has been defined by the International Headache Association as focal, progressive, worsening in the morning, worsening with coughing, or bending over, and transient, frequent episode [111].

Headaches are considered the "first sign" of brain tumors, but they are not the only complaints of cancer patients. A prospective study of 183 patients with brain tumors over a 2-year period identified 15 patients (8%) who had headache as their only complaint at presentation. Although only 8% reported headache as their only complaint. The occurrence of primary and metastatic tumors in headache patients was 60% and 40%, respectively, with no statistically significant difference [112].

The "classic" symptoms of cancer headache refer to headaches of severe intensity that appear on awakening, are of a dull and constant nature, and are accompanied by nausea and vomiting. Another prospective study noted some unusual findings. Morning headaches occurred in only 31.8% of patients and daily headaches occurred in only 10.6% of patients. Pain was often intermittent rather than continuous (88.4%) and typical headache duration was several hours (81.8%). These features were not typical of the classic appearance, but other more classic

features included throbbing in 63%, nausea and vomiting in 59.6%, and moderate in 90%. Headache progressed in patients with glioblastoma, astrocytoma, and metastatic tumors [112].

Patients with progressive headache were more likely to have glioblastoma or secretory adenoma compared with low-grade glioma. A meningioma was a symptom of tension-type headache [109].

Nausea and vomiting

Nausea and vomiting occur when the chemotactic trigger zone in the posterior region located at the base of the fourth ventricle is stimulated [113]. Vomiting usually presents with increased intracranial pressure but can also result from direct compression of the vomiting center by tumors of the posterior fossa, such as medulloblastoma and fourth ventricle ependymoma. It can also occur in the absence of elevated intracranial pressure in brainstem tumors affecting solitary nuclei. An acute headache followed by vomiting indicates increased intracranial pressure [112].

Distorted mental state.

Psychiatric and cognitive abnormalities can be specific or nonspecific. Certain findings involve aphasia, agnosia, and apraxia. Although these symptoms have local value, they are often confused with global cognitive impairment [112]. Cognitive impairment refers to a broad concept used to describe a variety of cognitive problems associated with impairments that often emerge with aging [114].

Nonspecific mental changes are one of the most common symptoms and are often subtle, especially in the initial course of the disease. Roughly 16-34% of patients exhibit irritability, personality changes, emotional lability, forgetfulness, lack of enthusiasm or spontaneity, and

slowed reactions that gradually progress to apathy or lethargy [115]. These symptoms do not reflect a tumor in a specific area of the brain, but if a tumor is present, it indicates a tumor in deeper structures and fibers.

Behavior may vary depending on which area of the frontal lobe is affected. For instance, dorsolateral frontal lobe tumors produce apathy, whereas orbitofrontal tumors produce disinhibition and impulsive behavior. Withdrawal and apathy can be mistaken for depression even though the patient denies being sad or depressed [116].

Aggressive and impulsive behavior is seen in amygdala lesions. In some cases, temporal lobe seizures are accompanied by behavioral disturbances. Studies describe tantrums in patients with temporal lobe glioma. Especially in primary central nervous system lymphoma, changes in behavior and personality appear as the main complaints [112] [116].

Papilledema

Papilledema is swelling of the optic nerve that connects the eye to the brain. This swelling is a response to increased pressure in or around the brain and has many causes [117].

Papilledema is a sign of increased intracranial pressure. Currently, it is rarely observed in patients at the onset of brain tumors. This is mostly due to the widespread availability of modern neuroimaging before tumors are advanced enough to cause papilledema. The mildest or acute cases may not result in vision changes. In some cases, an enlarged blind spot may be the only finding on examination. Papilledema, like headaches, is common in children and adolescents. This may be because the elderly has more room for tumors to spread due to brain atrophy, or because pressure is not transmitted to the intervertebral disc due to fibrosis of the optic nerve sheath in the elderly [112].

Papilledema due to increased intracranial pressure is usually bilateral but not symmetrical. Certain chronic diseases, such as frontal lobe tumors and olfactory groove meningioma, can rarely cause Foster-Kennedy syndrome. In Foster-Kennedy syndrome, there is optic nerve atrophy on one side of the tumor and chronic focal compression causes papilledema on the contralateral side. Due to increased intracranial pressure [112].

Seizure

A seizure is rapid, abnormal electrical activity in the brain. It can go largely unnoticed. In severe cases, the person may lose consciousness, or the body may shake and convulse [118]

Seizures are a common symptom in patients with brain tumors. Incidence varies between 30% and 100% and differs by tumor type, with slow-growing tumors being the most epileptogenic. Low-grade tumors may be more refractory than high-grade lesions [119]. In general, attacks that occur later in the clinical course respond better to treatment than those that occur earlier [120]. Seizures that are initially controlled but persist upon tumor recurrence are comparatively challenging to treat [121].

More than 50% of patients with glioma experience recurrent seizures during their disease, whereas 11% of patients with brain metastases and 19% of patients with neoplastic meningitis experience recurrent attacks during a much shorter lifetime [112].

4.2 Clinical presentation of the symptoms of brain tumors

The clinical presentation of brain tumors is confusing and varies greatly with tumor category, location, size, and growth rate as discussed above. From an etiological point of view, the clinical features can be divided into increased intracranial pressure and increased local pressure to characteristic of natural tissue damage. Till now, headache is the most frequently reported

symptom in patients. Headache is considered as a common medical condition and a common complaint for nearly half of those affected. Headache is the first symptom in most cases. In addition to headaches and seizures, other symptoms include nausea and vomiting, ataxia, visual disturbances, personality and behavioral changes, language disturbances, altered consciousness, sleep disturbances, drowsiness, fatigue, memory problems, Partial tingling and so on [110] Local symptoms in affected brain regions include:

Table (6): Local symptoms of brain tumor in affected regions of the brain [110].

Lobes of the brain	Symptoms encountered
1. Frontal	Personality & Behavioral changes Cognitive dysfunction Memory loss Contralateral motor loss
2. Parietal	Spatial Disorientation Difficulty in reading, writing, and naming. Aphasia Recognition problems
3. Occipital	Unilateral/bilateral vision loss Visual field defects Illusions Hallucinations Blurred vision
4. Temporal	Short-long memory loss Speech and language deficit Emotional changes (aggressiveness) Difficulty in understanding words
5. Cerebellum	Ataxia

	Difficulty in fine motor skills
6. Brain Stem	Difficulty in swallowing Facial tingling Double vision

4.3 Generalized behavioral symptoms.

The following is a list of common psychiatric symptoms that can be experienced by those diagnosed with a brain tumor: [116]

- Abusive behavior (verbal, emotional, physical)
- Anger
- Anxiety
- Apathy
- Confusion
- Difficulty in adjustment
- Delirium
- Delusion
- Depression
- Hallucination
- Impulsive behavior
- Sleep cycle disorientation
- Social retraction
- Hypomania
- Suicidal behavior

Chapter 5

Causes

Although the exact cause of brain tumors cannot be determined, several risk factors have been extensively studied [122]. The possible causes brain tumors are thought to arise when certain genes on the chromosomes of cells are damaged and stop working properly. These genes usually regulate the rate at which cells divide (if they divide), repair genes that repair defects in other genes, or cause cells to self-destruct if damage exceeds repair [123]. As the DNA of brain cells changes, new instructions are given to the brain cells. Bodies develop abnormal brain cells that grow and multiply faster than normal and, in some cases, live longer than normal. Then an ever-growing mass of abnormal cells takes up space in the brain [36]. In some cases, people are born with partial defects in one or more of these genes.

Even though only about 5-10% of people with brain tumors have a family history of brain tumors, there are some rare hereditary (passed from parent to child) syndromes associated with brain tumors which include: [124]

- Neurofibromatosis type 1 (NF1 gene)
- Neurofibromatosis type 2 (NF2 gene)
- Turcot syndrome (APC gene)
- Gorlin syndrome (PTCH gene)
- Tuberous sclerosis complex (TSC1 and TSC2 genes)
- Li-Fraumeni syndrome (TP53 gene)

In other cases, environmental factors like exposure to large amounts of radiation from X-rays or previous cancer treatment can cause further damage [125]. It is unclear why some people

develop brain tumors and others do not because of the 'environment'

As we know, when cells divide rapidly and the internal mechanism that controls their proliferation is damaged, they can eventually develop into tumors [126]. Another line of defence can be the body's immune system, which ideally would recognize and kill abnormal cells. Tumors produce substances that prevent the immune system from recognizing abnormal tumor cells, the ‘non-self’ cells from the ‘self’ cells, ultimately overcoming internal and external barriers to tumor growth [127].

A rapidly growing tumor may require more oxygen and nutrients than the local blood supply supplied to normal tissue. Tumors can produce substances called angiogenic factors that promote the growth of blood vessels. The growth of new blood vessels increases the nutrient supply to tumors, which eventually become dependent on these new blood vessels [128].

In the 19th century, Stephen Paget, an English surgeon who put forward the seed and soil hypothesis suggested that metastatic growth of a tumor depends on the interaction and affinity between cancer cells (seed) and distant specific organ tissue (soil). The surgeon claim that a nutrient microenvironment is essential for the proliferation of metastatic cells in distant tissues, this has also been supported by the theoretical background of modern cancer research [129]. He based the deep understanding of the complex and multifactorial mechanisms of metastasis formation upon 3 assumptions being: [130]

1. the presence of tumor heterogeneity, including morphologically and phenotypically distinct profiles of cancer cells with different proliferative, angiogenic, invasive and metastatic properties.

2. a metastatic process selective for tumor cells that perform all key steps of the metastatic cascade.
3. the metastatic potential of the tumor. This relies on several interactions and homeostatic mechanisms between the primary tumor and the tumor microenvironment.

Neuropsychiatric symptoms associated with brain tumors often have multiple causes. Often, they are a combination of: [131]

• Tumor localization (e.g., frontal lobe or medial frontal structures)
• Tumor damage - and its treatment - anatomical areas affected by the tumor
• age and general health;
• Other health problems and their treatment. Common examples are:
- Corticosteroids (e.g., dexamethasone)
- Antiepileptic drugs (e.g. levetiracetam)
- Biochemical and electrical changes in the brain due to tumors
- Brain changes due to treatment side effects > increased intracranial pressure
- Changes in cytokine levels
- Family history of mental disorders

Causes of brain tumor are predicted to be appearing in certain people having inherited or genetic conditions. Whereas, it can also be from environment, lifestyle or many other causes stated above. Research is ongoing in this area, but more extensive research is needed to apply this knowledge to potential therapeutics.

Chapter 6:

Risk Factors

A risk factor is anything that increases the risk of developing an illness or a disease, in this case, brain tumor. Risk factors often influence the development of brain tumors, but most of them do not directly cause them. Some people with multiple risk factors will not necessarily develop brain tumors whereas people with no known risk factors might develop brain tumors.

Risk factors for brain tumors are usually defined in analytical epidemiological studies that compare the risk of brain tumors in participants using cohort studies (participants with and without certain characteristics) and case control studies (participants with and without brain tumors) [132].

The cause of the risk factors is not clear in most people with primary brain tumors. Nevertheless, doctors have classified some factors that may increase the risk of a brain tumor. Some of the common factors that expose people to this risk include:

- ***Ionizing radiation***

Nowadays for both diagnostic and therapeutic purposes radiation is used. Ionizing radiation were found to be a potential cause for the occurrence of brain tumors, especially meningiomas, gliomas, and nerve sheath tumors. IARC has categorized ionizing radiation as a proven carcinogen [133]. It was studied that patients who received high doses of radiation in the head as children were exposed to a higher risk of developing brain tumors. CT scans, compared to other imaging tests, increase the risk of intracranial tumor progression as they produce higher radiation [132]. The atomic bombings of Hiroshima and Nagasaki exposed people to this harmful radiation which is why more cases of brain tumors in adults have been reported since

then. Increases in 5 cases per 100,000 (after 5 years) to 15 cases per 100,000 (after 20 years) incidences of meningioma were documented among A-bomb survivors.

- ***Radiofrequency electromagnetic radiations (RF-EMR)/ Non-ionizing radiation***

Even though mobile phones which initially invented emitted low levels of radio frequency electromagnetic radiation (RF-EMR), mobile phones today function on frequencies between 900 to 1800 MHz or more. The reason for cell phones to now emit such radiation is due to more advanced technologies of these phones being second, third and fourth generations. Using mobile phones directly exposes the human brain to high-frequency electromagnetic radiation [135].

Transmission of energy through radio waves is known as Radio frequency (RF) electromagnetic radiation (EMR). RF-EMR is non-ionizing radiation [136].

SAR parameter is the absorption rate of radio waves per unit mass, which is used to measure the potential harmful effects of RF exposure [137]. SAR is directly proportional to the dielectric field of tissue. Energy absorption in the head is determined by calculating the dielectric properties of the brain [138]. Even though the thorough mechanism of RF-induced tumors is still not quite known, some studies have shown noteworthy free radical activity in the brain. Free radicals are highly cytotoxic. These studies support the concept that being exposed to high-frequency electromagnetic fields creates free radicals inside cells that play an important role in DNA strand damages and disruption of normal cell function. Glial cells are more likely to transform into cancer cells due to DNA damage [139]. Thus, it can be proved that brain tumor risk is associated with mobile phone use.

Early technology cell phones with only first and second generation were introduced in 1990. In May 2011, IARC and WHO classified RF-EMF emitted from mobile phones as a “possible”

human carcinogen based on the IARC interphone study RF-EMF assessment of human carcinogenicity. [139][140]. A very interesting case-control study to show association between brain tumor risk and mobile phone use showed that ipsilateral users were exposed to a higher risk of developing temporal lobe brain tumors [140]. It was proven that regular mobile phone use was riskier than intercom use through a detailed study done by the Hardell Group in Sweden [141]. Other studies found an association of higher risk of brain tumor development with an increase in RF-EMF exposure duration. However, many epidemiological studies, failed to find any specific relation between brain tumors and cell phone use [142]. Improved assessments and further studies might find much useful associations between the emissions and cellphone usage in the future.

- ***Genetic factors***

Brain tumors are found to be associated with numerous familial cancer syndromes or inherited cancer syndromes [143]. These include Li-Fraumeni syndrome, neurofibromatosis, tuberous sclerosis, and Turcot syndrome [132]. What is common between this syndrome is that people inherit germline mutations in tumor suppressor genes. When the remaining copes of the tumor suppressor is mutated or suppressed generating cells the support growth that is when the tumors occur. There is increased risk for these people to develop cancer because tumorigenesis requires the accumulation of multiple mutations in cells and all these cells carry initial degrees of mutations [143].

Family clustering can be due to both genetic and environmental factors, as families often share common environmental influences in addition to common genes. Therefore, in addition to the known familial cancer predisposition syndrome, it has also been observed that brain tumors may occur more frequently in families [144].

Numerous researchers are looking into possible methods for testing for susceptibility genes because it is difficult to use unbiased screening for genetic risk factors. One of the earliest quality families examined was the glutathione S-transferase (GST) gene, which plays a role in the detoxification of environmental carcinogens [145]. Most studies find a significant association between the GST genotype and brain cancer risk [146].

Mixed results were yielded in finding the link between candidate genes to overall brain tumor even though there is evidence that genetic risk must be considered [132]. This happened due to the limited number of brain tumor patients available for these studies and the need for different genetic factors such that no single candidate factor has significant relevance. Environmental risk factors are inconsistent across populations and studies. Essentially, this amounts to too many variables and not enough subjects to determine statistical significance [143].

- ***Epigenetic modifications***

The study of genetic changes in chromosome is referred to as Epigenetics. These changes modify gene expression by turning them on or off. [147]. The hypermethylation of CpG islands which leads to silencing of tumor suppressor genes and promotes tumorigenesis is one of the epigenetic changes [148]. Tumors such as anaplastic astrocytoma anaplastic oligodendroglioma contain certain genes that undergo epigenetic changes [149]. Hypomethylation in gene results in abnormal expression [150]. In a certain brain tumor type, global hypomethylation of the genome was found to contributes to tumor development through three mechanisms, including loss of imprinting, promotion of genomic instability, and oncogene activation [141]. Another type of epigenetic change could involve position change of histone variants.

- ***N-nitroso compounds (NOC)***

NOCs has been categorized as highly carcinogenic by IARC. They contain nitrosamines and nitroamides. Some foods are richer in nitrosamines content compared to others, examples include beer and bacon [133]. Meat that has been cooked in high temperatures increase in NOC content [153]. Studies in animal models have shown that all animals are susceptible to the carcinogenic effects of NOC because these compounds can cross the blood-brain barrier in animals and act as potent carcinogens [133].

In humans, continuous intake of NOCs from food brings about carcinogenic effects in the body [153]. A large case-control study observing the relationship between pediatric brain tumors and maternal dietary intake of nitrites and/or nitrates during pregnancy was conducted and provided evidence for pediatric astroglia tumors. Cured and processed meats are found to be rich sources of preformed nitrosamines and NOC precursors. Studies determining tumor progression from cured and processed meats have reached contradictory conclusions. Studies also show plant-derived nitrites can cause gliomas [133].

- ***Hair dyes***

Hair dyes are thought to increase the risk of human tumors. Given that 10% of men (over 40) and 1/3 of women in Europe and North America use hair dye, this poses an alarming public health concern [154]. In a population-based case-control study of women in Nebraska to assess the association between personal hair dye use and glioma, non-permanent hair dye use was associated with brain tumors [155]. In a brief hospital-based case-control study investigating the relationship between synthetic hair dye use and brain tumors, there was no consistent evidence that long-term hair dye use causes meningioma, glioma, and acoustic neuroma. However, this study found a strong association with glioblastoma risk in women who used

permanent brown hair dye for 20 years or more [156]. A recent prospective cohort study of 117,200 women who had personally used permanent hair dye for 36 years found no significant association between permanent hair dye use and brain tumors [157]. The above studies do not provide conclusive evidence. Therefore, further studies are required to fully understand the association between hair dyes and brain tumors as studies done show contradictory results.

- ***Pesticides***

Some pesticides are known to be highly carcinogenic. Farmers have a statistically increased risk of brain tumors of up to 30%. Several active substances have been related with specific cancers [158]. A cohort study of French farmers found clear evidence linking exposure to agricultural pesticides to brain tumors. It was found that the incidence of brain tumors increased with exposure to carbamate pesticides. Another French study showed an association between the use of pesticide in vineyards and central nervous system tumors [133].

Toxicological examinations in research center assessing cancer-causing potential didn't yield cancer-causing results steady with detailed epidemiological discoveries. In epidemiological studies, it is challenging to quantify the variety of exposures that can be attributed to farming and pesticides. In the future, researchers will require inventive and novel exposure assessment methods [158].

- ***Reproductive and menstrual factors***

Gender differences in the incidence of brain tumors suggest that hormonal factors may be involved in the development of these tumors. The incidence of glioma is approximately 1.5 times higher in men than in women, while the incidence of meningioma is 1.5 times higher in women than in men [159]. Accounting for almost 75% of primary malignant brain tumors in adults, glioma was found to be the most common primary malignant brain tumor [160].

However, their biological importance is primarily based on their association with ionizing radiation [161]. Several studies have reported gender differences in the incidence of glioma. In the United States, the incidence of male glioma begins in childhood and adolescence and increases with age [159]. Various studies have shown that female sexual protection does not work until the age of 10 to 14, which approximately overlaps with the commencement of menstruation. The incidence of glioblastoma multiforme in women peaks between the ages of 50 and 54 and appears to decline later in life [161].

- ***Outdoor air pollution***

There are growing concerns regarding the probable impact of air pollution on the activation of microglia cells and chronic inflammation in the brain, although there is limited evidence of its carcinogenic effects. Air pollution and particulate matter (PM) were identified as human carcinogens by the IARC in 2012 [162]. For agents that can cross the blood-brain barrier, air pollutants may enter the brain through the systemic circulation [163]. Air pollution can adversely affect the central nervous system (CNS). It is caused by increased risk of stroke, decreased cerebral blood flow and cognitive function [164], but research is still ongoing into the carcinogenic effects of air pollution on malignant and benign brain tumors. However, epidemiological evidence for an association between exposure to outdoor air pollution and brain tumors is limited [165].

- ***Therapeutic doses of ionizing radiation***

Exposure to therapeutic doses of ionizing radiation is the only proven possible adjustable risk factor for brain tumors [166]. Mixed results have been obtained regarding exposure to diagnostic and therapeutic head and neck radiographs [139]. However, radiographs taken 15 to 40 years before diagnosis appear to increase the risk of meningioma [167]. A Finnish study

indicated that patients who had formerly received radiation therapy for brain tumors matured a second primary brain tumor more frequently than expected [168]. Higher incidence of meningioma was noticed in A-bomb survivors of Hiroshima which correlates with radiation dose to the brain [169]. Along with incidence of meningioma, the survivors were also seen to have higher rates of glioma, schwannoma, and pituitary tumors [169]. There are consistent and apparent results showing an association between ionizing radiation and brain tumor risk. However, because exposures to high levels of ionizing radiation are rare, only a minority of these exposures cause brain tumors [170].

Chapter 7

Diagnosis

Successfully diagnosing brain tumors at an early stage is crucial for optimizing treatment results and, therefore, patient survival [171]. Brain scans, a neurological examination, and a biopsy are frequently used to identify brain tumors. Doctors can use imaging studies to determine if the tumor is a primary brain tumor or cancer that has spread to the brain from another part of the body. Images of the human body's inside are produced using imaging tests. Medical imaging is the practice of seeing various human tissues and organs to track the body's normal and pathological morphology and physiology [172]. Factors that doctors may consider when choosing a diagnostic test:

- The kind of tumor suspected.
- Signs and symptoms detected.
- Age and general health
- Prior medical test results

Most brain tumors are discovered after symptoms arise. An internist or neurologist frequently makes the first diagnosis of a brain tumor. A physician with a focus on treating adults is known as an internist. A neurologist is a medical professional who focuses on issues relating to the brain and central nervous system.

The doctor may suggest the tests listed below in addition to getting a thorough medical history from the patient and doing a physical exam. These tests are used to detect the existence of brain tumors and, in certain cases, to determine their kind or grade [173]. The most popular and

preferable diagnostic modalities for identifying suspected primary brain tumors are computed tomography (CT) and magnetic resonance imaging (MRI) [172].

The most frequent method for identifying the kind of brain tumor when an MRI reveals the presence of a tumor in the brain is to examine the results of a tissue sample taken during a biopsy or surgery. The details of these tests and processes are provided below.

7.1 Magnetic resonance imaging (MRI)

MRI is a non-invasive technique for seeing the interior organization and some bodily functions (174). It employs non-ionizing electromagnetic radiation and doesn't seem to pose any risks from exposure. It uses radio frequency (RF) radiation to provide high-quality cross-sectional photographs of the body in any plane when a well-regulated magnetic field is present [175].

The patient is placed within a big magnet, creating a reasonably strong external magnetic field, and this creates the MR image [176]. This makes many atoms in the body, including hydrogen, align their nuclei with the magnetic field before an RF signal is applied [177]. Body energy is emitted, recognized, and utilized by a computer software to create the MR picture [176].

MRI scanners are well adapted for imaging the body's soft tissues or non-bony portions. They do not employ x-rays' harmful ionizing radiation. With MRI, muscles, ligaments, and tendons, as well as the brain, spinal cord, and nerves, are viewed comparatively more clearly [174]. To scan joint injury, soft tissue injury or internal organ damage, MRI is frequently employed [178]. Aneurysms and tumors can also be identified with MRI. They can be used to distinguish between white matter and grey matter in the brain. Gives a close

view at brain architecture and see which parts of the brain "activate" (use more oxygen) when doing different kinds of cognitive activities. It presents a possible new standard for evaluating neurological health and risk for neurosurgery and is utilized to increase our understanding of how the brain is organized [179].

7.1.1 How MRI works.

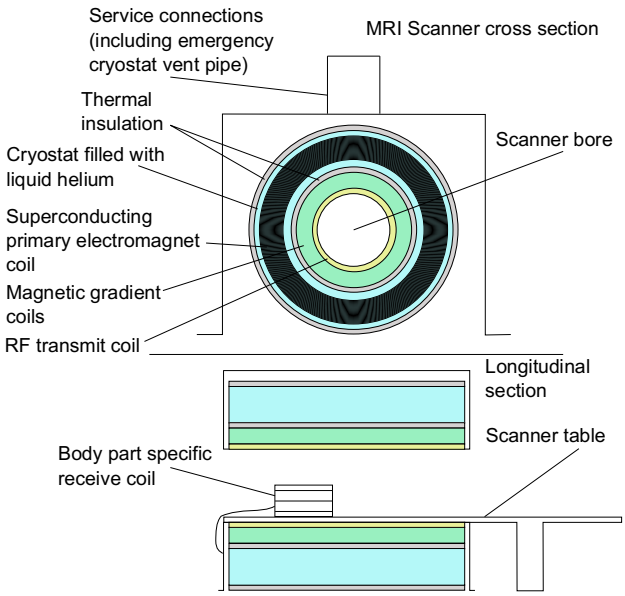

Figure (21): An MRI machine with labelled segments illustrated [180]

By using the magnetic characteristics of the body, magnetic resonance imaging (MRI) may provide precise pictures of any portion of the body. Due to its high concentration in water and fat, the hydrogen nucleus (a single proton) is employed for imaging [177].

The hydrogen proton may be compared to the earth, which has a north and south pole and spins on its axis. In this way, it functions like a tiny bar magnet. These hydrogen proton "bar magnets" rotate in the body normally with their axes randomly aligned [177].

The axes of the protons align when the body is positioned in a high magnetic field, such as an MRI scanner. A magnetic vector that is aligned along the axis of the MRI scanner is

produced by this uniform alignment. Different field strengths, typically between 0.5 and 1.5 tesla, are available for MRI scanners [174].

The magnetic vector is deflected when more energy (in the form of a radio wave) is introduced to the magnetic field. The sought-after element (in this example, hydrogen) and the intensity of the magnetic field affect the radio wave frequency (RF) that causes the hydrogen nuclei to vibrate [177].

A series of gradient electric coils may electrically change the magnetic field's intensity from head to toe. By changing the local magnetic field in these tiny increments, various slices of the body will resonate as different frequencies are applied [181].

The magnetic vector returns to its resting state when the radiofrequency source is turned off, which results in the emission of a signal (also a radio wave). The signal in question is what generates the MR pictures. To increase the signal's ability to be detected, receiver coils are wrapped around the affected body part and employed as aerials. After plotting the received signal's strength on a gray scale, cross-sectional pictures are created [181].

Water molecule and how it contains two hydrogen atoms on the sides of one oxygen atom. Hydrogen nucleus is comprised of positive charge a proton that is rotating on its axis and functions as a small magnet. Protons align with the magnetic field in the MRI scanner, some "up", and a little less "down" [182]. Only the little amount of additional "up" protons' magnetic field remains after the entire magnet field created by all the hydrogen protons virtually cancels out. Using MRI, we can quantify this minor magnetic field**.** The "up" protons flip away from the magnetic field as they absorb the RF energy when an RF wave or pulse is switched on that has the same frequency as the proton's regimented frequency [183].

7.1.2 Report interpretation

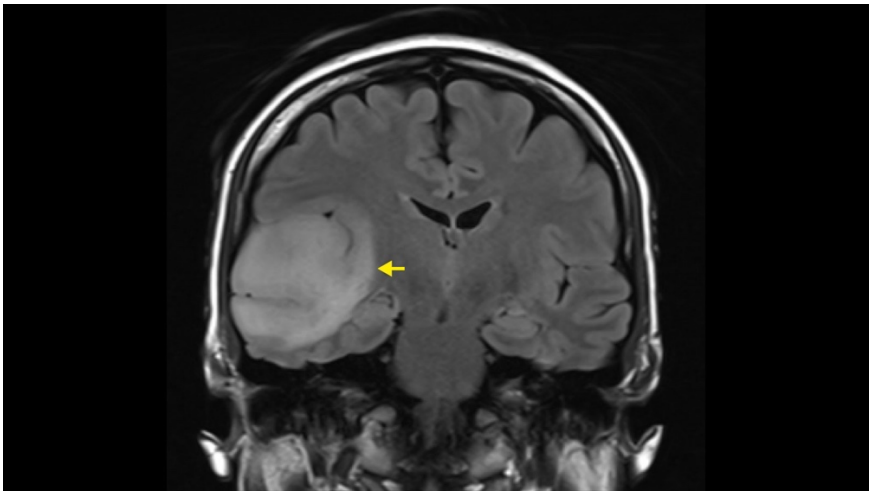

Figure (22): MRI scan of a patient [184]

The findings need to relate to clinical features and detailed clinical questions. This is because even though MRI scans highlights information regarding the position and size of abnormality areas in the brain, with the help of various detailed and specific clinical histories would the strongest clues be provided for the best diagnosis. The scan above from patient was diagnosed to have brain tumor astrocytoma/oligodendroglioma [184].

7.3.1 Advantages of MRI

Magnetic imaging resonance (MRI) has been used comprehensively as a diagnostic tool within both clinically and in research. Compared to other diagnostic tools, its advantages include it being non-invasive and it uses no ionizing radiation [185]. Hydrogen which is a key component- is the only atom that MRI is sensitive to, in almost all cases, thus there are almost no limitations to the kind of biological samples that can be imaged [185].

Because hydrogen atoms in various tissues and substances have somewhat varying chemical and magnetic environments, this results in contrast in an MRI image [186]. As a result, when radio waves in the form of brief (radio frequency) RF-pulses are injected into the item being investigated, they will react to them somewhat differently. This enables the detection of pathogenic alterations deep into an organ [187]. This biggest benefit of MRI over most other imaging methods is in this area.

One of the strongest advantages of high field magnetic resonance imaging systems is the high ratio, the Signal to Noise Ratio (SNR). The ratio is almost twice in MRI than any other imaging. High ratio means more signal and therefore better display in shorter time with better image quality and greater 3-D resolution. Respectively shorter time means increased comfort for the patient to co-operate impeccably to avoid pseudo-motion [188].

MRI scanners provides radiation free medical imaging. They use body's natural magnetic properties instead of using radiation like the other imaging techniques. They use sound waves to create images. For this reason, they can cater to more patients like to pregnant women or to babies [177].

An MRI scanner is built to accommodate the whole human body. Compared to other medical imaging examinations, the head-to-toe scan has several major benefits. Doctors can see early indications of sickness or anomalies since the MRI can scan the complete body and provide cross-sectional pictures. An MRI can be used to find cancer in its early stages anywhere in the body [189].

7.1.4 Risks of MRI

MRI scanners are narrow tunnels where patients are expected to lie down and hold their position cautiously for best imaging results. This has been proven to be very uncomfortable for

specially patients with claustrophobia. Patients who have claustrophobia are terrified and feel trapped in or confined in enclosed spaces [190]. This circumstance hinders patient acceptability, slows down workflow, and wastes critical scanning time [191].

MRI equipment's are economical unfeasible as they are expensive to purchase, maintain and to operate. Their hardware and software are still being developed to cope with different patient conditions (claustrophobia) and needs and for the betterment of differentiation as bone, teeth, air and metallic objects all appear black [175].

The MR environment could be dangerous for patients with specific implants, mainly because of the movement or dislodgment of objects made of ferromagnetic materials [192] but also because of heating and the induction of electrical currents, which could pose risks to patients with implants or external devices like pacemakers or neurostimulation devices etc. that are electronically triggered [193]. Patients and others using such implants may be at risk in the MR environment due to translational attraction and torque caused by the magnetic field.

A noise level of more than 100 decibels during the measurement is one of the potential dangers of MRI, in addition to the generation of circular currents in the body caused by switching field gradients and the heating of human tissue by powerful RF radiation [175].

Patients might experience an adverse response to the contrast material or get a skin infection where the injection was made [194]. Also, benign, and malignant tumors cannot always be distinguished by MRI, or a false-positive result may occur. Requires radiologist expertise [195].

7.2 CT scan

A computerized x-ray imaging procedure known as "computed tomography" or "CT" involves aiming a narrow beam of x-rays at a patient and quickly rotating it around the

body [196]. This produces signals that are processed by the machine's computer to generate cross-sectional images, or "slices," of the patient. Tomographic images are the name given to these slices, which can offer a clinician more in-depth information than standard x-rays [197]. When various progressive cuts are gathered by the machine's PC, they can be carefully "stacked" together to frame a three-layered (3D) picture of the patient that takes into consideration simpler distinguishing proof of essential designs as well as could be expected growths or irregularities [196].

In a cranial CT scan, what can be expected are images of the skull, brain, paranasal sinuses, ventricles, and eye sockets to be seen in detail. Another name for Ct scan is known as CAT scan. There are several other names for a cranial CT scan, such as brain scan, head scan, skull scan, and sinus scan [198].

For diagnosing and characterizing infections, malignancies, traumatic injuries, skeletal problems, and vascular abnormalities, CT is frequently used as a first-line imaging procedure [199]. Alzheimer's disease, brain tumors, bleeding, brain traumas, and other serious brain illnesses are all diagnosed with head CT scans. Additionally, it is utilized in radiosurgery, stereotactic surgery, and CT-guided surgery to treat brain tumors, arteriovenous malformations, and other conditions [200]

CT scans also aid in locating blood clots, excess fluid or infections which helps doctors to guide treatments plans and procedures like biopsies, surgeries, and radio therapies [201].

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7.2.1 How CT scan works

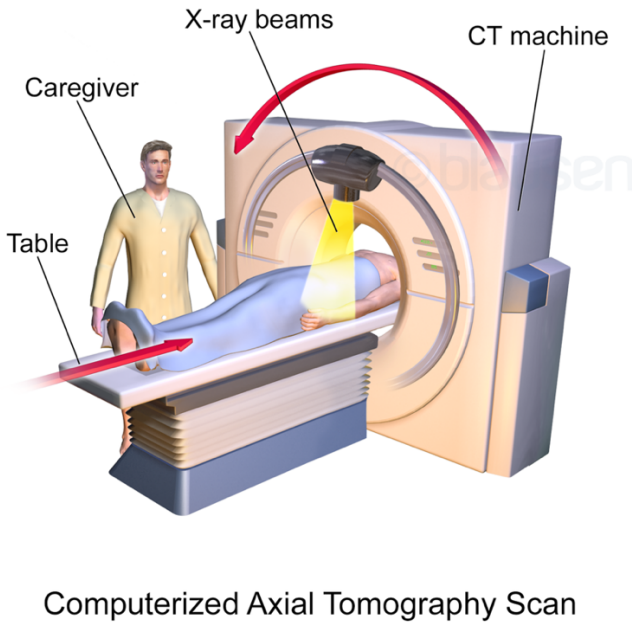

Figure (23): Main components of a CT scan machine [202]

Motorized X-rays sources are employed in CT scanners that keeps rotating around the circular opening of the gantry (donut-shaped component) [200]. The X-ray tube rotates around the patient shooting narrow beams of X-ray through the body, the bed carrying the patient slowly moves through the gantry. Special digital x-ray detectors, which are placed immediately across from the x-ray source, are used in CT scanners in place of film. The detectors catch the x-rays as they leave the patient and send them to a computer [203].

CT computer uses standardized mathematical techniques to construct a two-dimensional image slice of the patient as the x-ray source rotates once every entire revolution [196]. CT scans, which are two-dimensional images of three-dimensional physical things, are commonly used.

In order to create the photographs, electrical energy (moving electrons) must first be converted into X-ray photons, which must then be passed through an object and detected before being converted back into electrons. The density of the object has an inverse relationship with the number of X-rays that travel through it. CT imaging of objects (like people) reveals portions of varying densities [199]. Depending on the CT equipment being used, the thickness of the tissue shown in each imaging slice might change, although it typically varies from 1 to 10 millimeters [196].

After finishing a full slice, the picture is saved, and the motorized bed is slowly lowered onto the gantry. Then another picture slice is created by repeating the x-ray scanning procedure. This procedure is repeated until the required number of slices has been gathered [204].

The computer may either display the picture slices separately or stack them to create a 3D representation of the patient that displays the skeleton, organs, tissues, and any anomalies the doctor is hoping to see [204].

Contrast dye is necessary for some CT scans to facilitate diagnosis. When consumed, contrast dye makes the stomach and bowels more visible. Using a cannula, contrast dye may be used to illuminate the body's arteries and veins [205]. The modalities and physics of the imaging equipment will determine the best way to employ contrast. Computed tomography (CT), which is a result of radiographs, shows how a target tissue depletes an energy signal as it goes through the tissue. The physical characteristics of the energy beam and the target are among the factors influencing the signal loss [206].

7.2.2 Report interpretation

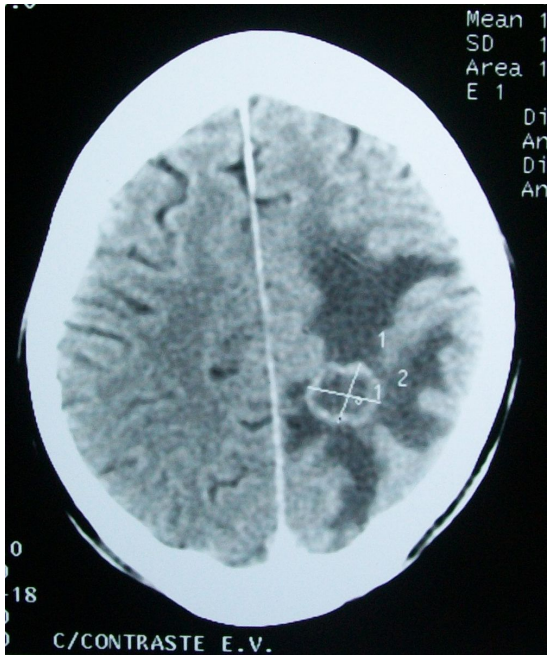

Figure (24): CT scan (with contrast) of a patient with brain tumor [207].

The figure (24) above is a Computed Tomography scan (with contrast) of a brain. It shows the appearance of a tumor at the left temporo-parietal lobe of the brain. Tumor suspected to be metastasis [207].

7.2.3 Advantages of CT scan

For many different reasons, CT is a frequently utilized diagnostic and screening imaging technology. The scan assists in evaluating head injuries, severe headaches, dizziness, and other symptoms of brain tumors, bleeding, aneurysms, and strokes. It particularly helps health care professionals to plan radiation therapy for brain cancer [208]. CT can be done more rapidly and for less money [199]. The development of CT has given doctors knowledge to prevent needless laparotomies, saving millions of dollars in healthcare expenses [196].

The last stage of diagnosis frequently involves the use of CT scanning, therefore extra testing is not required, preventing the need for rigorous invasive procedures. It aids in deciding whether surgery is necessary. Its' built-in high contrast resolution makes it possible to

distinguish between tissues with physical density differences of less than 1%. It can get rid of the overlapping of images of objects outside the region of interest [200].

It quickly replaced cerebral angiography as a quick, highly accurate approach to identify brain masses and damage from head trauma [196]. These methods employ recurrent reconstruction algorithms to provide pictures with reduced image noise and improved diagnostic quality at lower radiation exposure [209].

The method of identifying the stage of cancer and diagnosing cancer is substantially improved by CT scans. CT scanning aids in allocating the patient to the proper hospital care regions [210].

After a CT scan, no radiation remains in a patient's body. There should be no immediate side effects from the x-rays used for the CT scan [209].

7.2.4 Risks of CT scan

The ionizing radiation that is used in a CT scan has the potential to harm biological tissue [211]. CT scans can have a radiation dose that is 50 to 1,000 times higher than that of standard X-rays [212]. They are the source of the most radiation that is given to the population, after natural and environmental sources. About half of all medical radiation is generated by CT scans.

The radiation dose of a CT scan ranges from 1.0 mSv to 27.0 mSv. They should be performed if the benefit far outweighs the risk [211]. An adult abdominal CT exposes the patient to 10 mSv, while natural and environmental exposure is approximately 3.0 mSv per year [212]. However, the exposure is 20 mSv during a neonatal abdominal CT [211]. 1 mSv=1 mGy. There is a 5-percent chance of dying from cancer for every 1.0 mSv of exposure, according to estimates. Thus, a radiation dose of 100 mSv will have a 0.5% risk of cancer. Due to the vulnerability of the developing organs and the cumulative lifetime exposure, this radiation

exposure is especially harmful to children [212]. Following the ALARA (as low as reasonably achievable) principle, exposure should be limited. Numerous assessments ought to be stayed away from. They ought to be finished assuming that the advantage by a long shot offsets the risk [211].

Contrast agents may trigger mild, itchy, rash-like allergic reactions; whereas in non-serious conditions, adequate hydration prior to the post-contrast injection will eliminate contrast from the body [213]. However, severe reactions like bronchospasm and anaphylactic reaction can occur. The probability of a fatal reaction is approximately 1 in 100,000 [214]. Kidney failure caused by the iodine contrast material can occur in 2 to 7% of patients, with a greater risk for those with former kidney disease [215].

7.3 Positron emission tomography (PET) or PET-CT scan

Positron transfer tomography (PET) is an approach that measures physiology by examining blood flow, metabolism, neurotransmitters, and radiolabeled drugs. PET provides a quantitative analysis [216]. Radioactive means that the chemical will decompose without external influence. Radioactivity is released upon decay. This activity will be used to create a PET image. PET scanners can accurately track the path through the body and measure the radiation emitted by the body. A variety of cross-sectional images are created from these results. A computer can create spatial (three-dimensional, 3D) images from these cross-sections [217]

One of the most popular imaging tests that allows doctors to look for disorders in the human body is the PET scan. The most frequent uses of PET scans are to find cancer, cardiac issues, and brain diseases [218]. This technique is based on detecting the radioactivity released after injection of a small amount of radiotracer into a peripheral vein. Tracers are administered as

intravenous injections and are usually labeled with oxygen-15, fluorine-18, carbon-11, or nitrogen-13. The total radiation dose is like that used in computed tomography [216].

A PET-CT hybrid consists of two scanning devices. PET scanner and X-ray computed tomography (CT). PET-CT offers the possibility of assessing disease through simultaneous analysis of function and morphology [219].

Currently, the most used PET radiotracer (18 F) fluorodeoxyglucose (FDG) plays an important role in oncology [219]. However, it also has numerous clinical applications in cardiology, neurology, and psychiatry. The goals of tumor imaging remain lesion detection, lesion characterization, malignant lesion grading, and treatment response assessment. Staging includes lesion localization, assessment of vascular proximity, and detection of nodal and distant metastases [220].

Some of these goals can be better achieved using high-resolution anatomical imaging methods such as CT, while others are his PET-based molecular imaging. can be achieved better with PET helps distinguish between benign and malignant lesions, aids in accurate staging, reliably detects recurrence, and can be used to assess response to therapy for malignant lesions [221].

Clinically, FDG-PET (F-18 PET) is used for initial staging, assessment of response to therapy, assessment of malignant transformation of low-grade tumors, and differentiation of residual/recurrent tumors from post-treatment changes [222].

7.3.1 How does PET scan work

PET scanners use radioactive tracers to measure various metabolic processes in the body [223]. Various changes such as metabolism, blood flow, and regional chemical composition can be analyzed [224]. Radiotracers can be injected, swallowed, or inhaled, depending on the body part to be examined, and depending on their affinity, the tracer will adhere to various tissues

of the body. Areas of high activity will have more uptake and will appear as bright spots on the image. The unstable nuclei of the radioactive tracer emit positrons that combine with neighboring electrons to produce gamma rays. Gamma rays are captured by the scanner's detector ring. The computer then uses this data to create a 3D image of her with tracers inside her body. Different tracers are used depending on the target [217]. Tracers can be administered intravenously, orally, or by inhalation. It takes time for the tracer to spread throughout the body. Contrast can be administered intravenously or orally when PET-CT is performed. The position depends on the part to be scanned. The PET machine has a central hole through which the patient passes. The first image is usually a investigation image to assess if the positioning is correct. Sometimes you may even need to hold your breath. The scan will take 30 minutes to 1 hour [217].

A positron is the antiparticle of an electron with the same mass and charge. After being emitted, the positron has some kinetic energy, but it is lost through multiple collisions with electrons in nearby tissues. When the positron's energy is completely or almost completely lost, it combines with an electron. This eventually forms a short-lived compound, namely positronium. The positronium produced in this way has a short lifetime and eventually annihilates, converting its entire mass into energy, thereby emitting two photons in opposite directions as shown in the diagram (40) above. This ensures that energy and momentum are conserved. The unique property of simultaneous emission of two annihilated photons forms the basis for the detection and localization of positron emitters using a new technique called coincidence detection [225].

A scintillation detector and a photomultiplier tube are placed on opposite sides of the positron emission source. The signal is then fed to a separate amplifier and energy discrimination circuit. The result of this process is the detection of coincident events and the identification of annihilation events somewhere along the line connecting the two detectors [225].

7.3.2 Report interpretation

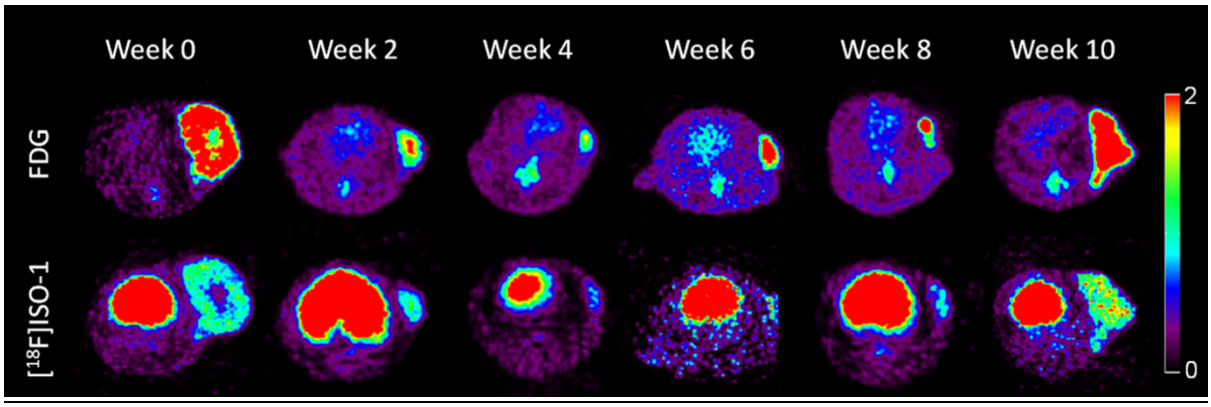

Figure (25): FDG PET/CT scan of brain of an operated high-grade glioma, post radiotherapy case [220].

From the figure (25) shows several brain scan imaging using unique sigma-2 receptor ligands and FDG ligands. The scans are related to tumor growth and cancer progression over a period of 10 weeks [220].

7.3.3 Advantages of PET scan

The physics of radiation and the detection of co-occurring photons give PET imaging a unique opportunity to achieve both very high sensitivity and accurate estimation of in vivo concentrations of radiotracers. It has been widely adopted as an important clinical technique for applications in oncology, cardiovascular medicine, and neurology [224].

PET measures glucose utilization in different parts of the body and assess blood flow and oxygen consumption in different parts of the brain to understand stroke and dementia. Tracking of chemical neurotransmitters (such as dopamine in Parkinson's disease) can also be achieved using this technique [216].

PET scans are superior to other tests because they show metabolic changes occurring at the cellular level in organs and tissues, whereas other imaging techniques like CT scans and MRIs cannot reveal problems at the cellular level [218].

The greatest advantage of PET is the follow-up examination to detect residual or recurrent disease. The timing of his PET scan after treatment is an important factor in improving the specificity of his PET in distinguishing tumor from acute inflammatory changes after treatment [220].

According to the level of radiation exposed to, PET uses substances that are broken down very quickly in the body and excreted out of the body via the kidneys. This process is faster with adequate hydration. The half-life of FDG, the most used radiolabeled glucose analogue, is just under 2 hours. This means that after about 110 minutes only half of the original radioactivity remains, a quarter is remained after 4 hours [226].

7.3.4 Risks of PET scan

A single PET scan contains approximately the same amount of radiation that a person would receive in a year from natural radiation in the environment [226].

PET-CT contains radioactive material and there is radiation exposure. The effective radiation dose of 18F-FDG is 14 mSv. Potential side effects of radiation remain. In a typical PET scan, the radiation dose is significantly lower, in the 8 millisievert range, about the same as the radiation dose from natural sources such as the sun. PET-CT uses higher radiation levels in the range of 24 mSv. Pregnant women should not have a PET scan unless necessary, as the radiation can affect the fetus. Breastfeeding women should limit close contact with infants or pregnant women to a maximum of 12 hours [217].

Allergic reactions to tracers can occur. PET/CT scans require additional tracers. This can be detrimental for people with kidney disease or those who have elevated creatinine levels due to medications they are already taking [227].

This test may also include discomfort for patients who are claustrophobic or who experience discomfort when using needles. Injections may also cause bleeding, bruising, swelling, and other symptoms [227].

7.3 Collecting and testing a sample of abnormal tissue (biopsy).

The surgical process of brain biopsy is beneficial in the treatment of individuals with suspected neoplastic lesions [228]. Alzheimer's disease, different types of infections, inflammation, and other brain diseases. Examined under a microscope, the biopsy sample provides the information required for treatment [229].

During a brain biopsy, a sample of brain tumor tissue is removed for laboratory analysis to diagnose abnormalities of the brain [229]. The sample is frequently obtained by a surgeon during brain tumor removal surgery. A sample may be taken using a needle if surgery is not an option. Stereotactic needle biopsy is a technique used to remove a sample of brain tumor tissue using a needle. A stereotactic needle biopsy may be done for brain tumors in hard-to-reach areas or very sensitive areas within your brain that might be damaged by a more extensive operation. Your neurosurgeon drills a small hole into your skull. A thin needle is then inserted through the hole. Tissue is removed using the needle, which is frequently guided by CT or MRI scanning [230].

The biopsy sample is then viewed under a microscope to determine if it's cancerous or benign. Sophisticated laboratory tests can give doctors clues about your prognosis and your treatment options. This process usually chosen when doctors are unsure about diagnosis results.

After a thorough examination, a brain biopsy is frequently advised yet another method to help make the diagnosis. This retrospective cohort analysis's objectives are to assess the open brain

biopsy's sensitivity in this patient group, compare the findings to the preoperatively assumed diagnosis, and determine if the biopsy result substantially affects the course of therapy [231]

There are different types of biopsies depending on the states of brain tumor. The difference between them is the way the surgeon carries out the process biopsy [232]

- a biopsy as part of the operation to remove the tumors- As a part of the procedure to remove the brain tumor completely or partially, known as a craniotomy. Surgeon removes skull's bone. This provides a window for them to extract a tumor sample.
- a needle biopsy- small hole is drilled on to the skull, thin needle is inserted into the tumor through it. A guided biopsy helps if tumor is very deep inside the brain or if it has spread widely across the brain. A CT scan or MRI scan serves as the guidance for a guided biopsy.

The two major approaches to a guided needle biopsy are as follows.

1. Neuro navigation: Before having a CT or MRI scan, markers are implanted. The markers are used by a computer to pinpoint the tumor's precise location.
2. Stereotactic biopsy: a head frame is used to help the surgeon direct the needle to the tumors.

- an open biopsy- carried out if a bigger sample is required or there is a higher risk of bleeding. To make it simpler to reach the tumor, your surgeon removes a little portion of the skull. Sometimes this technique is referred to as a small craniotomy.
- a neuro endoscopy- May be used to collect tissue from or near the ventricles, the fluid-filled regions in the brain. To view into the brain and collect tissue samples, a long tube known as an endoscope is used.

If a brain lesion is present, such as an abscess or tumor, the tissue cells removed during the biopsy can reveal its kind and whether it is benign (not cancerous) or cancerous (malignant). Doctors can prescribe a course of action by identifying the precise cell type.

Biopsies are less intrusive than open craniotomies for tumor excision, yet no procedure is without danger. Additionally, they are less complicated. A biopsy might result in bleeding, brain swelling, seizures, a stroke, an infection, blood clots, or anesthesia-related complications [233].

7.5 Cerebral arteriogram, also called a cerebral angiogram.

A cerebral angiogram is an x-ray or series of x-rays of the head that show the arteries in the brain. X-rays are taken after special dyes called contrast agents are injected into the major arteries of the patient's head [234].

7.6 Lumbar puncture or spinal tap

A spinal tap is a procedure in which a sample of cerebrospinal fluid (CSF) is taken with a needle to look for tumor cells, blood, or tumor markers. Tumor markers or biomarkers are substances found in above-average amounts in the blood, urine, spinal fluid, plasma, or other body fluids of people with certain types of tumors. Patients are usually given a local aesthetic to numb the lower back before surgery [235]. It is also used to measure intracranial pressure and administer medication and diagnostics [236].

7.7 Myelogram

Myelography describes the injection of an intrathecal contrast agent for imaging pathology of the spinal canal [237]. Myelography is recommended to find out if the tumor has spread to the cerebrospinal fluid, other parts of the brain, or the spinal cord. For myelography, dye

is injected into the cerebrospinal fluid that surrounds the spinal cord. The dye shows up on x-rays and can outline the spinal cord, helping doctors look for tumors. This test is run only occasionally [238].

7.8 Biomarker testing of the tumor

Molecular cancer biomarkers are measurable molecular indicators of cancer risk, cancer development, or patient outcome. These include germline or somatic genetic variations, epigenetic signatures, transcriptional alterations, and proteomic signatures. These indicators are based on biomolecules such as nucleic acids and proteins that can be detected in tissue samples from tumor biopsies or, more simply and non-invasively, blood (or serum or plasma), saliva, buccal swabs, stool, urine, etc. [239].

7.9 Neurological, vision, and hearing tests

A neurological examination is an assessment tool used to determine a patient's neurological function. This is advantageous in many respects, as it allows localization of neurological disorders and helps classify or rule out differential diagnoses. Neuropathy manifests itself in many ways, including cognitive/behavioural, visual, motor, and sensory symptoms. Certain warning signals during testing enable early detection of life-threatening neurological disorders, as well as diseases that can adversely affect quality of life [240].

7.10 Neurocognitive assessment

This includes an in-depth assessment of all key brain functions such as: memory storage and retrieval, verbal expression and reception, arithmetic, manual dexterity, and the patient's general health. These tests are performed by a licensed clinical neuropsychologist.

This professional prepares a formal report to compare with future evaluations and to identify specific problems that treatment may solve [241].

7.11 Electroencephalography (EEG)

Electroencephalography (EEG) is an important tool for studying electrical activity in the brain. Despite the development of more advanced imaging techniques, EEG remains an essential subclinical tool for seizure assessment. This activity provides an overview of electroencephalography (EEG) testing, including techniques, indications, contraindications, and clinical significance [242]. EEG is a non-invasive test that measures electrical activity in the brain using electrodes placed on the outside of a person's head. Used to monitor for possible seizures [243].

7.12 Evoked potentials

Evoked potentials use electrodes to measure the electrical activity of nerves and can often detect acoustic schwannoma, a benign brain tumor. This test can help remove tumors growing around important nerves [244].

Chapter 8

Treatment

Treatment of a brain tumor is done based on it being cancerous (malignant) or non-cancerous (benign). The kind, size, grade, and location of the brain tumor all affect the available treatments. Surgery, radiation treatment, radiosurgery, chemotherapy, and targeted therapy are all potential options. General health must be taken under consideration while deciding the course of treatment.

8.1 Surgery

Craniotomy: An intracranial operation, known as a craniotomy, is a surgical procedure in which a portion of the skull is temporarily removed to expose the brain [245]. Craniotomy can be frequently used to treat a number of:

- Brain tumors
- Aneurysms
- Arterio-venous malformations
- Subdural empyema's,
- Subdural hematomas, and
- Intracerebral hematomas

The bone flap, a portion of bone, is removed using specialized instruments and machinery. After the brain operation is finished, the bone flap is briefly removed, held at the operating room instrument table, and then replaced [246].

Craniectomy: The technique is referred to as a craniectomy if the bone flap is removed or not inserted back into the skull during the same procedure. The bone flap is repositioned in a decompressive craniectomy for malignant brain edema a few weeks after the brain edema has subsided [247].

Cranioplasty: the surgical operation used to rebuild and reattach the bone flap to the skull during a subsequent surgery [248].

Few risks involved in brain tumor surgery: [249]

- High anesthesia risks include old age and serious medical conditions.
- A poor state of functioning
- Increased morbidity factor
- Multiorgan failure and severe systemic collapse
- Abnormalities of coagulation, bleeding and infection
- Non-compliance from patience
- Refusal from patient

Other risks may depend on the part of your brain where your tumor is located. For instance, surgery on a tumor near nerves that connect to your eyes may carry a risk of vision loss.

8.2 Radiation therapy

Radiation therapy is an important part of the treatment of primary and metastatic brain tumors. Due to the proximity of vital structures and normal brain parenchyma, the central nervous system "CNS" cannot exist nearby. Radiotherapy is associated with side effects, such as neurocognitive impairment, that must be weighed against the benefits of improved tumor control [250].

Utilizing targeted X-rays or subatomic particles for both curative and palliative cancer care is known as radiation therapy. Both inside and outside can receive it. The most typical kind of radiation treatment, commonly referred to as "teletherapy," uses an external radioactive source to direct and shape energy toward the desired target. Contrarily, brachytherapy is the process of implanting naturally existing radioactive sources that emit large doses of radiation and degrade over time in a focused location [251].

External beam radiation can focus just on the area of your brain where the tumor is located, or it can be applied to your entire brain (whole-brain radiation). Whole-brain radiation is most often used to treat cancer that spreads to the brain from some other part of the body and forms multiple tumors in the brain [250].

Radiotherapy traditionally used X-rays, but this new form of treatment uses proton beams. Proton therapy gives doctors more precise control over radiation. It may help treat brain tumors in children and tumors that are very close to sensitive areas of the brain. Proton therapy is not as widely used as his conventional X-ray radiotherapy [251].

Risks of radiotherapy related with the use of ionizing radiation include: (1) Induction of brain tumors primarily through the diagnostic use of radiation. (2) Cognitive decline after treatment of childhood brain tumors, as an example of a long-term effect that is often neglected to emphasize the second primary cancer. (3) Proliferative and invasive changes that occur in tumor cells that have survived radiotherapy [252]

Side effects of radiation therapy depend on the type and dose of radiation you receive. Common side effects during or immediately following radiation include fatigue, headaches, memory loss, scalp irritation, vomiting and hair loss etc. [253].

8.3 Radiosurgery

Stereotactic radiosurgery is a non-invasive, ambulatory surgery that does not require general anesthesia. the first step is to find the target [254]. Stereotactic radiosurgery is a type of radiotherapy that is becoming an increasingly popular neurosurgical option for the treatment of tumors, vascular disease, and functional disorders (such as movement disorders and trigeminal neuralgia) [255].

In SRS, multiple focused beams of high-energy X-ray (gamma) rays or proton beams are delivered to discrete, radiologically defined treatment volumes. Radiation output is highly conformal [256]. By using multiple intersecting radiation beams, the treatment area receives a therapeutically prescribed high dose, while the surrounding normal brain tissue receives a relatively low dose. Rapid decay of radiation to surrounding tissue limits toxicity and side effects, ensuring safety [256]. Stereotactic radiosurgery works by radiation-induced DNA damage by ions and free radicals [257].

Radiation causes vascular endothelial damage and white matter demyelination, leading to necrosis [258]. Acute effects that occur within a few weeks after treatment may be due to cerebral edema and disruption of the blood-brain barrier. Symptoms include headache, nausea, and vomiting [259].

8.4 Chemotherapy

In addition to surgery and radiation therapy, drugs are often used to treat cancer. A classic example of this is chemotherapy, which uses drugs called cytostatic. The purpose of these drugs is to prevent cancer cells from dividing uncontrolled [226]. Chemotherapy is used to treat several types of brain tumors, including primary central nervous system lymphoma,

medulloblastoma, brain metastases, and malignant glioma [260]. The aim of chemotherapy is to inhibit cell proliferation and tumor growth and prevent invasion and metastasis. However, the toxic effect of chemotherapy is caused by its impact on normal cells. Inhibition of tumor growth can occur at multiple levels within the cell and its environment [261].

Chemotherapy can be administered as neoadjuvant, adjuvant, combination, and metastatic therapy. Neoadjuvant therapy is treatment given before primary treatment. Adjuvant therapy is treatment given in addition to initial treatment that can slow or eliminate the growth of hidden cancer cells. Adjuvant therapy is now the standard for breast, lung, colon, and ovarian cancer. Combination treatments, such as chemotherapy and radiation, are used before surgery to shrink tumors and cure cancers such as head and neck, lung, and anal cancers. Multitargeted or combination therapy is superior to monotherapy for most cancer treatments [262].

Most chemotherapy drugs are metabolized and excreted in the liver or kidneys. Some chemotherapy drugs are toxic to the liver and kidneys. In such cases, toxic concentrations can build up in the body and cause organ dysfunction. Therefore, it is important to consider dose adjustments in these organ failure patients [263]. Chemotherapy drugs often have side effects. The side effects of chemotherapy usually reflect its mechanism of action. Cytotoxic chemotherapy often targets DNA and protein expression in both cancer cells and normal host cells. Because most chemotherapy drugs work on rapidly growing cells, they tend to affect rapidly growing cells. Toxicities commonly associated with such agents include myelosuppression, nausea, vomiting, gastrointestinal side effects, mucositis, alopecia, infertility, infertility, and infusion reactions. In addition, immunosuppression increases the risk of infection [262].

8.5 Targeted drug therapy

Targeted therapy aims to deliver drugs to specific genes or proteins specific to the cancer cell or tissue environment that promote cancer growth. The effectiveness of this therapy lies in the targeted delivery of therapeutic agents to the disease site while minimizing unwanted side effects caused by normal tissue [264].

It is often used in combination with chemotherapy and other cancer treatments. Targeted therapies include the development of drugs that block cancer cell proliferation, promote cell cycle regulation, induce apoptosis and autophagy, and deliver targeted toxic substances to cancer cells to destroy them. will be Targeted therapy uses monoclonal antibodies or low-dose oral drugs [265].

Chapter 9

Rehabilitation after treatment

Recovery from brain surgery can be stressful for patients and their loved ones. Brain surgery is a major issue both physically and mentally for the body to handle [266]. Brain tissue that is damaged but not destroyed by a stroke or head injury can gradually regain function. Rehabilitation can expedite and achieve recovery, which can take anywhere from six months to several years. Brain tissue that is destroyed can't recover its capability; thus, different parts of the brain take over the duties of the damaged tissues. Rehabilitation assists this learning process. Rehabilitation is started as soon as people are medically stable as its extent and rate of recovery of function is uncertain [267].

Initial side-effects post-surgery might include dizziness, weakness, poor balance, and speech issues whereas long term side effects may include memory issues, speech issues, difficulty in walking and behavioral changes etc. [266].

To get back to daily functions and activities, some patients may require rehabilitation after brain surgery [266]. Tumor size and location, as well as how much tumor has been removed, can affect a person's recovery. Patients with tumors in expressive areas, such as on or near the motor or language areas, usually require physical therapy, speech therapy, or both [268]. Depending on the specific requirements of each patient, rehabilitation may involve collaboration with various therapists like speech therapists, occupational therapists, physical therapists, and other specialists:

Physical therapy assists in acquiring new muscle strength or motor skills. If a brain injury causes weakness or paralysis in a limb, the therapist moves the limb or encourages the person to move them. This helps keep joint mobility and strength. The person is expected to engage in other activities like moving in bed, rolling over, repositioning, and sitting up right. Therapy will be successful when the patient is being able to get out of bed safely and independently and sit in a chair or wheelchair [267].

Coordination exercises may also be required. The therapist uses (constraint-induced movement therapy) to immobilize the unaffected limb. For example, a person with a partially paralyzed arm can wear a sling on their healthy arm while performing repetitive daily activities such as eating, washing clothes, personal hygiene, writing, and opening doors. This helps rewire the brain to use weakened or paralyzed limbs for faster recovery [267].

Few other points that physical therapists help with for rehabilitation: [269]

- Control exercises for head or neck
- Sensory stimulation
- Soft tissue mobilization, stretching and massage
- Balance in sitting or standing whether sitting or standing
- Gait and stair training
- Providing an exercise program at home

Occupational therapy assists in returning to work or other regular activities like walking, improving coordination and balance and reducing spasticity (involuntary muscle contractions). [271]. They make greater use of the results of psychological research to encourage participation in meaningful activities, especially leisure activities, as they are strongly correlated with health, well-being, and quality of life [271]. These recreational

interventions are more therapeutic than conventional therapy as they provide opportunities to employ multiple body systems and skills, such as: Proprioception, Vestibular, Visual, Cognitive, Emotional, Muscle Tone, Range of Motion, Endurance, and Overall Motor Patterns and Fine Motor Coordination [271].

From cooking to exercise, occupational therapists work with clients to set personal goals and help them achieve them through personalized therapeutic intervention strategies [272].

Speech therapists can assist patients who have trouble speaking. Three types of speech and language disorders might be common in people who get a brain tumour surgery- dysarthria, aphasia and apraxia of speech each affecting muscle coordination of the mouth, speaking difficulty and movement difficulties respectively [273]

Speech therapy exercises may include the following techniques:

- problem solving,
- memory recall
- organization of thoughts and words, and other activities to improve cognitive communication
- conversation tactics to improve social communication.
- breathing method
- strengthen mouth muscles
- games such as puzzles, and word games related to the "function" of the brain

Cognitive therapy- Strokes and other brain injuries, especially concussions, can impair thinking (cognitive) abilities. People can have problems with orientation, attention and concentration, perception, comprehension, learning, organizing thoughts, problem solving, memory, language, and more. What problems a person has depends on the injury [274].

Cognitive rehabilitation is a very time-consuming process that must be tailored to each individual situation and requires individualized treatment. The goal is to retrain the brain and teach it how to compensate for problems. For example, work such as tying shoelaces is broken down into simple parts and practiced. Verbal, visual, and tactile (touch) cues such as verbal cues, gestures, and color-coded items also help learn and remember how to complete tasks [274].

This study found that brain tumor patients who underwent intensive rehabilitation showed significant functional improvements in motor, balance, cognitive, and ADL functions. It was not affected by malignancy [275]. With further development of treatment options, the need for intensive rehabilitation therapy is ever increasing. However, intensive rehabilitation therapy appears to be inadequate for patients with brain tumors, especially when the tumor is malignant. Physical therapists may be reluctant to prescribe rehabilitation therapy to brain tumor survivors because malignant brain tumors have poor survival rates and high recurrence rates [276].

Scherrer et al. [277] studied functional recovery in brain tumor patients undergoing rehabilitation and reported functional recovery in 6 of 13 patients.

In summary, brain tumor patients who underwent intensive rehabilitation after surgery experienced improvements in motor, cognitive, and ADL function. Despite poor survival and high recurrence rates for patients with malignant brain tumors, family caregivers expressed high satisfaction with functional improvement after intensive rehabilitation therapy. These results suggest that postoperative rehabilitation may be beneficial in patients with brain tumors, despite their poor survival rates, and should be considered regardless of tumor pathology [268].

It is vital for healthcare providers to address the rehabilitation needs of their patients, as rehabilitation services could lead to cognitive benefits, increased functionality, and overall improvement in the health-related quality of life. The rehabilitation type and setting should be catered to the individual needs of patients and their caregivers, and when considering the devastating prognoses some brain tumors carry, the benefits of rehabilitation should be weighed against the time spent in a healthcare facility [278].

From diagnosis to surgery, side effects of treatment to recovery, and even relapse, many patients and caregivers feel anxious and alone. Support groups can improve their mental health and quality of life by providing information, emotional support, and resources. Support groups consist of patients and caregivers in similar life situations who meet regularly to share experiences, exchange practical tips, and build support networks. Self-help groups are usually free and can be conducted in person or online [279].

A variety of support services are available to patients in the Neuro-Oncology program [280]. These include:

- Counselling: A dedicated social worker provides support and assistance to brain tumor patients and their families.
- Brain Tumor Support Group: Patients and their families share their experiences while gaining support and knowledge.
- Rehabilitation: Professionals work with patients to maximize their quality of life during and after cancer treatment.
- Home service: Patients can remain independent while enjoying a range of clinical and supportive services at home.

Chapter 10

Pediatrics Brain Tumor

The most frequent form of solid childhood cancer are the pediatric brain tumours. [281]. They are the main contributor to fatalities from childhood cancer [282]. The prognosis for other high-grade tumours is still dismal, despite improvements in surgical and adjuvant therapy that have increased 5-year survival rates for children with low-grade brain tumours to over 75% [283].

Despite advances in medical knowledge, there is no direct cause of brain tumor development. To begin with, it could be a combination of genetic and environmental factors in the development of brain tumors. Family history may play a part in it as well, various studies have stated an association between brain tumors and siblings. The age of the parents at birth can also play a role. Studies have shown that offspring of women over the age of 40 are at increased risk of developing brain tumors (astrocytoma and ependymomas). Some studies have suggested a link between exposure to childhood infections and brain tumors. High doses of radiation are associated with malignant brain disease for instance if the child is exposed to radiation for treatment of leukemia, then they will be at risk of developing brain tumors. This topic is still controversial [282].

The incidence of childhood brain tumors varies among different countries. Infections range from 1.15 to 5.14 per 100,000 children, with the highest incidence reported from the United States [284]. The incidence of CBT ranges from approximately 0.3 to 2.9 per 100,000 live births in different parts of the world [285].

Among the most frequently reported types of brain tumors in the congenital group, teratoma was seen to be the most common type (26.6%-48%). followed by astrocytoma (7.4% to 28.8%),

choroid plexus papilloma (3.7% to 13.2%), embryonic tumor (3% to 13%), craniopharyngioma (5.6% to 6, 8%), followed by ependymoma (4.4%) [286].

Pediatric and adult brain tumors differ not only in incidence, but also in histology, molecular pathology, localization, and outcome [287]. However, some typical childhood brain tumors can also occur in adults.

As for the symptoms that usually occur in children, it was found in a Danish study of 46 consecutive pediatric hospitalizations (≥11 years) with CNS tumors, headache, vomiting, and fatigue were the most common symptoms [288]. Another Danish study of 55 children (mean age at diagnosis 8.4 years) found that most (59%) of them had infratentorial tumors, vomiting (87%), headache (all 69% of children developed focal, 39% arousal), ataxia (35%) and seizures (20%), with symptoms commonly reported by patients [289]. 8 Among 60 children (mean age at diagnosis 5.8 years) admitted to two hospitals in Japan, the most common symptoms were vomiting (24%), headache (17%) restlessness (10%) and paralysis (10%) [290]. In the multicenter group, the most common signs in 166 patients were vomiting (72%), psychomotor regression (60%), and ataxia (60%) [291].

Surgery is the main treatment for both children and adults. The surgical approach chosen is similar for adults and children and depends on the location of the individual tumor. [292]. However, in children, special care should be taken to protect against parasites. Children tend to develop posterior fossa syndrome (called 'posterior fossa syndrome'), a combination of mutism, cranial neuropathy, and emotional lability after nematode manipulation, although this phenomenon is much less frequent in adults. is not seen [293]. To avoid excessive cerebellar traction, the terovera approach is recommended for midline tumors and can be performed either in the prone, park bench, or sitting position, depending on the surgeon's preference [294]. In addition to CSI, chemotherapy is also recommended for MB, regardless of tumor subgroup or

patient age [295]. Young children are given multiple drugs for chemotherapy. However, adolescents and adults are less tolerant and more toxic to chemotherapy compared to children and may require individual adjustments to standard protocols [296].

Post brain tumor surgery rehabilitation for children is the same as adults which include physiotherapy, occupational therapy and speech therapy etc. Approach into how these therapies are conducted by specialists differ in terms execution. For instance, children are tutored or are engaged in fun exercises like drawing and crafting etc, which makes them express and communicate better as they find it harder to communicate compared to an adult.

Studies confirm the beneficial effects of comprehensive rehabilitation on functional outcomes in children who remain disabled after treatment for primary brain tumors [297].

Types	Epidemiology	Symptoms	Diagnosis	Treatment	References
Choroid Plexus Carcinoma	Rare, cancerous, malignant and begin near brain tissue.	Excess fluid in the brain, irritability & nausea	Physical exam, Brain imaging tests, Genetic tests	Surgery, Chemotherapy, Radiation therapy	[282] [298]
Craniopharyngioma	Rare, non-cancerous, benign, begins near the pituitary gland, secretes body controlling hormones	Changes in vision, fatigue, excessive urination, headaches	Physical exam, blood tests, imaging tests		•
Embryonal tumors	Cancerous, malignant, start in the embryonic cells in the brain	Headaches, nausea, tiredness, double vision, instability & seizures	Neurological exam, imaging tests, biopsy, lumbar Puncture	Surgery to relieve fluid build-up in the brain & remove tumors, radiation & chemotherapy	•
Ependymoma	Form in the brain or spinal cord, begin in ependymal cells	Headaches, seizures	Imaging tests, neurological tests, lumbar Puncture	Surgery, radiation therapy, chemotherapy	•
Glioma - **Astrocytoma** - **Ependymoma** - **Glioblastoma** - **Oligodendroglioma**	Starts in the brain or spinal cord, slow growing, non-cancerous	Headache, nausea, vomiting, confusion, memory loss, irritability, speech difficulty	Imaging tests, neurological tests, biopsy	Surgery, radio and chemotherapy	•

Table (7): Types, epidemiology, symptoms, diagnosis, and treatment of various types of peadrtic brain tumor.

Medulloblastoma	Cancerous, begin at the back part of brain (cerebullum)	Dizziness, double vision, poor coordination	Neurological tests, imaging tests, tissue sample testing, removal of cerebrospinal fluid for testing	Surgery to relieve fluid buildup in the brain, radio and chemotherapy	
Pineoblastoma	starts in the brain's pineal gland (centre of brain), gland produces a hormone called melatonin	Headache, sleepiness, eye movement changes	Imaging tests, biopsy, removing cerebrospinal fluid for testing	Surgery to relieve fluid buildup in the brain, radiation therapy, chemotherapy, radiosurgery	

	Brain tumor in adult	Brain tumor in children	References
Most common type	Glioma (Grade IV)	Glioma (Grade I) Medulloblastoma	[299]
Location of tumor formation	Higher parts of the brain affecting memory and, language and thought	Lower parts of the brain which affect movement and co-ordination	[300]
Symptom	Similar in both	Similar in both	[303]
Risk Factor	Mostly involve alterations in DNA (mutations) and lifestyle	Unknown causes of deletion or over-expression of genes	[301]
Diagnosis	Similar in both	Similar in both	[302]
Treatment	Low doses of chemotherapy, types of drugs vary	High doses of chemotherapy, types of drugs vary	[301]
Post treatment	Physical therapy needed more	Tutoring is involved as school-age child needs help to cope with changes in memory and thinking	[302]
Side-effects	Manageable	Long-term side effects involved	[301]
Survival rate	Lower	Higher	[300]

Table (8): Major differences between adult and childhood brain tumors

Chapter 11

Brain Tumor and Bangladesh

In Bangladesh, neurosurgery has been practiced for a while. In 1970, with just six beds, Professor Rashiduddin Ahmed founded the first Neurosurgery section at the Institute of Postgraduate Medical Research (IPGMR). After 2000, neurosurgery advanced quickly on both a private and a governmental basis. In today's time, with the availability of investigations, diagnostic tools, operating rooms, and good neuro-anesthesia, neurosurgeons have expanded their knowledge to include vascular, pediatric, endoscopic, spinal stabilization, stereotactic, and stem cell therapies [304].

The number of people diagnosed with brain tumors in Bangladesh is steadily increasing. Every year more and more cases of brain tumors are detected in our country, which affect people of all ages [305].

Neurosurgeons specializes in the diagnosis and surgical treatment of neurological disorders such as birth defects, trauma, tumors, brain or spinal cord infections, and stroke. Surgical treatment like a craniotomy, which is an operation where part of the skull is removed to perform brain surgery. After removing the tumor, the surgeon fills the hole in the skull with the patient's own bone [305].

Below are some examples of hospitals in Bangladesh both private and government owned with well-known neurosurgeons: [306]

Private owned:

- Bangladesh specialized hospital (Dhaka)
- Square Hospital (Dhaka)
- United Hospital (Dhaka)
- CSCR Hospital
- Impulse Hospital (Dhaka)
- Popular Diagnostic Centre ltd (Around Bangladesh)
- Evercare Hospital (Dhaka)
- Ibn Sina Hospital (Around Bangladesh)
- Bangladesh Specialized Hospital (Dhaka)
- Mount Adora Hospital (Sylhet)

Government owned:

- Dhaka Medical College Hospital (Dhaka)
- National Institute of cancer Research Hospital
- Shaheed Suhrawardy Medical College and Hospital
- Dhaka Shishu Hospital (Dhaka)
- Bangabandhu Sheikh Mujib Medical University Hospital (Dhaka)
- National Institute of Neuroscience & Hospital (Dhaka)
- Chittagong Medical College (Chittagong)
- Mymensingh Medical College Hospital
- Rajshahi Medical College Hospital
- Rangpur Medical College Hospital
- Khulna Medical College Hospital

Hospitals in Bangladesh has wide range of diagnostic tools and tests available as well as treatment facilitates some of which include the following diagnosis and treatments: [307].

Diagnosis:

- X-rays
- CT scans
- MRI
- EEG
- EMG & NCS- tests
- Evoked Potential Studies
- Lumbar Puncture: Spinal Tap
- Muscle Biopsy and Histopathology service

Treatments:

General neurosurgery that includes:

- Surgery for all head and spinal injuries, intracranial hemorrhage, congenital cranial and spinal malformations, epilepsy, brain and spine infections, etc.
- Cerebral aneurysm clipping
- Cranio-vertebral junction pathology surgery
- Cerebrospinal fluid (CSF) leak repair
- Cerebrospinal fluid (CSF) shunt
- Intracranial pressure monitoring
- Skull deformity cranioplasty
- Microdiscectomy, laminectomy, laminoplasty, and foraminotomy
- Nerve and muscle biopsy

- CSF Resistance outflow study

Neuro-oncology surgery: All types of brain and spine tumors are offered, including skull base tumors. Available surgeons have expertise in meningiomas, pituitary adenomas, and vestibular schwannoma. Chemotherapy facilities also provided.

Pediatric Neurosurgery: Treatment of neurological disorders in children and adolescents offered. Surgeons specialized in surgery for brain and spine tumors, injuries, shunts, cranial, epilepsy etc**.**

Neuro-intensive care & Neuro anesthesia: Specialized care to patients with life-threatening acute neurological disorders and injuries provided. Examples of such conditions include stroke, traumatic brain and spinal cord injury, subarachnoid hemorrhage, aneurysm, autoimmune disease, and movement disorders such as Parkinson's disease, multiple sclerosis, and Gallian-Barré disease etc.

Neuro Rehabilitation: pre- and post-operative rehabilitation prescribed to patients who need them.

Rates for diagnostic tests for the head provided by privately owned hospitals (Square Hospital, Dhaka and Anwar Khan Modern Medical College Hospital, Dhaka, Dhaka) in Bangladesh: (Dr. Mohammed Tahmid Kazi, Personal Communications).

Table (9): Price list for diagnosis of brain tumor in private hospital in Bangladesh

No.	**Diagnostic test**	**Price range** in Taka (৳)
1.	Head X-ray	400-850/-
2.	Brain MRI	7000-15,500/-
3.	Head CT scan (without contrast)	4000-7500/-
	Head CT scan (with contrast)	~10,500/-
4.	EEG	2000-2500/-
5.	Brain PET-scan	3000-5000/-
6.	Nerve conduction study	8000/-
7.	Biopsy (depending on location)	6000-12000/-*

Prices for diagnostic tests for the head provided by government owned hospitals in Bangladesh (Dhaka Medical College):

Table (10): Price list for diagnosis of brain tumor in government hospital in Bangladesh

No.	**Diagnostic test**	**Price range** in Taka (৳)
1.	Head X-ray	150-250/-
2.	Head CT scan (without contrast)	2000/-
3.	Brain MRI	3000-4000/-
4.	Brain PET-scan	2000/-
5.	EEG	1500-2000/-
6.	Nerve conduction study	~3500-4000/-
7.	Biopsy (depending on location)	3000-7000/-

For treatments like Surgery, Radiosurgery, Chemotherapy, Radiation therapy type of brain metastases and its severity, its grade, its location in the brain and to the degree it has spread, and the types of drugs used will depend on the amount of money to be charged which are usually done upon consultation with patients. For treatments like neurosurgery, cost will depend on the type of surgery being done and the surgeons who is doing it as prices vary on different surgeons.

The table below shows an average cost of diagnosis and treatment of brain cancer in different cities in Bangladesh: [305]

Table (11): An estimated price list of brain tumor diagnosis and treatment in Bangladesh

Cities in Bangladesh	Cost in Taka (৳)
Dhaka	650,000/-
Chittagong	663,000/-
Khulna	676,000/-
Rajshahi	659,750/-
Gazipur	682,500/-
Sylhet	689,000/-
Mymensingh	702,000/-
Barisal	672,750/-
Rangpur	666,250/-
Comilla	679,250/-
Narayanganj	692,250/-

The cost above is an average price of investigations like USG and X-ray, diagnostics like CT scan, MRI/PET-CT scan, surgery (depending on type of lesion) followed by histopathological examination like chemotherapy or radiotherapy.

According to a study run in the department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University, (BSMMU) Dhaka from February 2002 to December 2005. Thirty-five patients were selected to evaluate the outcome & prognosis of metastatic brain tumors. In this following prospective study, it was found that, highest age of incidence of tumours were above 60 years. Male predominated than female (60.00%). Among the clinical features the most common sign was hemiparesis (34.28%). The commonest site of lesion was in frontal region (34.28%). Histopathological reports showed adenocarcinoma 40.00%, small cell carcinoma of

lungs 28.57%, squamous cell carcinoma 22.85%, follicular carcinoma of thyroid 5.71%. Treatment options were surgery, radiotherapy, and chemotherapy. Sixty percent patients were improved after treatment. Highest survival rate was 3 to 6 months with treatment (31.42%). This study revealed that commonest type of brain metastases was adenocarcinoma and primary site of lesion was lungs. Best option of treatment was surgery plus radiotherapy and longest survival rate of 1 year was in 20.00% cases [308].

Chapter 12

Discussion

The term "brain tumor" describes a diverse set of neoplasms that arise from the meninges and intracranial tissues and have growths ranging from benign to malignant. Each form of tumor has its own biology, course of therapy, and causes, and each is brought on by a unique set of risk factors. Due to their location in the brain, their capacity to infiltrate locally, and their propensity to develop into malignancy, even "benign" tumors can be fatal. This complicates the categorization of brain tumors and makes it difficult to describe the epidemiology of these diseases.

Because they are so frequent, brain tumors necessitate that general practitioners have a working knowledge of how to diagnose and treat them. Meningiomas, glioblastomas, and intracranial metastases are the most frequent types of brain tumors. Anywhere along the neuroaxis, the central nervous system might develop metastases, which call for extensive multidisciplinary treatment including neurosurgery, radiation oncology, chemotherapy etc. Meningiomas are meningeal tumors that are often benign and are treated surgically, with radiation treatment and chemotherapy only used in high-risk or refractory cases. The most prevalent and severe primary malignant brain tumor is glioblastoma, which has a limited response to associated chemoradiation therapy as standard of treatment.

Bangladesh has 142 million citizens, making it the seventh most populated nation on earth. In Bangladesh, there are 13 to 15 lakh cancer patients, with roughly 2 lakhs receiving a cancer diagnosis for the first time every year. Overall, the two most common malignancies in men are lung cancer and mouth-oropharynx cancer. Stomach cancer and esophageal cancer are other cancer forms. Breast cancer and cancer of the uterus in women are the most common types.

Lung cancer, esophageal cancer, and mouth and oropharynx cancer are other cancer kinds that afflict women. In the various regions of the nation, there are 16 pediatric oncologists and around 150 skilled clinical oncologists at work [309].

Brain tumors are not the most prevalent tumor in Bangladesh yet but the little knowledge, data information and low awareness about the whole issue in general can be alarming. Due to the increase in digitalization now, between 2000 and 2021, there were more mobile-cellular subscribers in Bangladesh. The number of mobile subscribers in Bangladesh increased to 184.44 million in 2021 from 176 million the year before [310]. As mentioned above, mobile phones are an associated risk factor for brain tumor as they directly expose the human brain to high frequency electromagnetic radiation [135]. Due to most local citizens having less realization on the precautions needed to deal with to be preventive of such a big illness, the rates of brain tumor occurrence potentially peak.

Another risk factors that the people of Bangladesh could be very much exposed to recently could be air pollution. Again, as mentioned above in Chapter 6, air pollution and particulate matter (PM) were identified as human carcinogens by the International Agency for research in cancer in 2012 [162]. The air quality in Dhaka also reaches an annual average of 90 g/m3 of PM2.5, or a 168 - Unhealthy Air Quality Index, according to the most current World Health Organization statistics [311]. Increased demand for housing, automobiles, and a boom in all industries following population growth could be the main focus for the country's pollution levels especially in the capital city. While there are still many areas in Bangladesh being serene and green and not falling under the category for fully being polluted, with its expanding population, a solution to these disastrous levels of smoke, haze, and pollutants in the atmosphere must be addressed.

Primary brain tumors arise in more than 100 different varieties, each with a unique range of symptoms, prognoses, and therapies. More than any other type of cancer, brain tumors can have profound and life-altering effects on a patient's physical, cognitive, and psychological health. And despite years of study, survival rates for brain cancer haven't altered much in recent years, despite notable advancements in many other tumors [312]

Although treating a brain tumor can be exceedingly difficult, recent advances in diagnostics and therapy have increased the survival rate. Low- and middle-income nations like India and Bangladesh have worse cure rates for children with brain tumors because of underdiagnosis, inaccurate clinical evaluation, and a lack of access to the right radiological, neurosurgical, and radiation treatments. Due to financial limitations, thorough registration of brain tumors and reliable data collecting are uncommon; as a result, the true incidence of this illness is unknown.

Even in India, being a third world country, the cost of brain tumor surgery is typically a fraction of the cost of the same surgery or treatment in the US or other developed countries. Brain tumor surgery is usually completed on the same day, making it a cost-effective treatment option compared to other traditional surgeries. And when compared similarly to developed countries, these treatments are often twice as expensive as in India. As brain tumor treatment is cheap in India, many international patients come to India for treatment [313]. The reason for this increase is that India is home to some of the best brain surgeons in the world. In addition to well-trained neurosurgeons, India boasts a professional and well-trained surgical and post-operative care team, as well as a world-class surgical and hospital infrastructure capable of handling complex cases at an affordable cost. On average, the cost of brain tumor surgery in India can range from about 240,000 rupees ($3,000) to 480,000 rupees ($6,000) [314]. Which is half of what is needed in Bangladesh.

In terms of post- surgery rehabilitation, first world countries have better facilities for it compared to our third world nations. For example, as informed by Mr. Tanzim Ahmed, Physiotherapist (MSc, BSc) from Melbourne Australia stated that in Melbourne, if complications are serious, a patient may be sent to a specialized neurological rehab center/clinic for up to six months to rehabilitate themselves (eg. NeuroRehab Allied Health Network Melbourne). If the complications are not so serious, the patient can just stay at hospital 3-5 days to undergo rehab at the hospital upon discharge. All hospitals in Melbourne, whether private or public offer inpatient rehab and have at least one physiotherapist, speech therapist and occupational therapist in one ward. Whereas, as stated by Mr. Aminul Islam Tuhin Physiotherapist (CMU, Life Care Medical center, Dhaka) says that currently at Centre of Rehabilitation for paralyzed (CRP) Mirpur is providing rehabilitation for stroke and other disabilities and other various center around Bangladesh providing physical therapy for brain and spinal cord related injuries but no post-operation rehabilitation.

Chapter 13:

Conclusion

Neuroscience is an interdisciplinary sector of science. It is the understanding of the nervous system and its development [1]. Neuroscience also involves various diseases, disorders, and injuries of the nervous system. Our nervous system has two major components- the central nervous system and the peripheral nervous system [4]. They both make up the control center for our body which is responsible for movements, thoughts, and automatic reflexes to the environment as well as internal processes like homeostasis, digestion, breathing and sexual development [5]. Our nervous system is one of the most complex systems in the human body as they communicate and are connected to other body systems to maintain the overall physiological well-being of our body [5].

The brain, being the most complex and fragile part of the body, directs and co-ordinates actions and reactions of the body [6]. Different lobes of the brain coordinate different functions. It has 5 senses- feel, touch, sight, hearing and taste. It has constant messages coming in and going out constantly via peripheral nerves [7].

Brain tumors are masses of cells which grow uncontrollably when there is no need for it or persist in the body when not required [62]. They can be con-cancerous (benign) or cancerous (malignant) but both types need treatment [9]. The kind of treatment option required depend on the type of tumor, its size and location. Tumors can arise from brain cells or somewhere else in the body that spreads to the brain as secondary tumors [64]. There are many types of brain tumors but the most found globally are gliomas in adults and medulloblastomas children. In studies done at Bangladesh, Astrocytomas were found to be most common in adults and low-rated medulloblastomas were found to be most common in children.

Symptoms involved are commonly headaches, nausea, and body balance issues [9]. But other symptoms involved include seizures [118], eyesight issues [117], mental instability [112] etc. In Bangladesh, studies show headaches, seizures and vomiting to be the most common symptoms.

Risk factors increase risk of developing an illness or disease therefore they influence the development of brain tumor. Such risk factors were found to be ionizing radiation, radiofrequency electromagnetic radiations, genetic factors, epigenetic modifications, and ionizing radiation from therapy treatments etc. The validates risk factors associated found through epidemiological studies were ionizing radiation in both adults and children, history of allergies in mostly adults and genetic factors in mostly children [315].

Diagnosis for brain tumors could be done by imaging tests like MRI, CT scans and PET scans [172], biopsies, lumbar puncture, myelograms etc. PET scans are usually used to detect areas of high metabolism and detect cancerous cells while CT and MRI scans provide detailed information about the location and extent of cancer [316]. MRI scans are chosen over CT or PET scans because of its non-invasive and safety properties along with the highest resolution image it provides and for its benefit of measuring tumor size. Diagnostic tests are chosen based on the kind of tumor suspected, symptoms associated, general health of the patient and prior medical test results. The other diagnostics are usually needed after the initial diagnosis done with imaging tests.

Treatments of the brain tumors involve surgery, radiation therapies, radiosurgery, chemotherapy, targeted therapy etc. They type of treatment required depend on the kind, size, grade, and location of the brain tumor [317].

Rehabilitation after treatment help patients to get back to their daily functions and activities [266]. Physical, speech and cognitive therapies help recover patients to fully recover and make them stable again [268].

Pediatric brin tumors differ from adult brin tumors in terms of location, symptoms, risk factors, diagnosis, treatment, side effects and survival rates. Pediatric tumor forms are more responsive to adjuvant radiation and chemotherapy than adult tumor types are. Based on age and the degree of therapy, the child's side effect spectrum is wider: Increased risk of severe long-term side effects impacting neurologic, endocrine, and cognitive function is associated with radiation therapy [318].

In Bangladesh, approximately 1,50,000 people die from cancer each year, according to a report. A comprehensive update report from 2013 revealed the presence of 1.3-1.5 million patients, with an annual addition of 0.2 million [319]. In the various regions of the nation, there are approximately 150 qualified clinical oncologists and 16 pediatric oncologists working. 19 hospitals provide regular cancer treatment, and the oncology and radiation therapy departments also have 465 hospital beds attached that serve as indoor or day care facilities for chemotherapy patients [309].

There are many hospitals in Bangladesh both in private and government sectors providing brain tumor diagnosis, treatment. Private hospitals provide much more facilities and quality service on the detection and treatment of various types of brain tumors therefore charge more compared to government hospitals with limited tools and technology and standard of service. The total cost of treating a brain tumor in Bangladesh starting from its detection to its management is more than it is compared to a third world and neighboring country like India.

13.1 Limitation

Due to the low incidence, primary malignant brain tumors are rarely diagnosed in primary care populations. The age-adjusted incidence of the most common type, glioma, is between 4.7 and 5.7 per 100,000 people [321]. Despite improvements in treatment, outcomes remain poor, and even though brain tumors account for less than 2% of all cancers, they account for the most lost life years of any type [322]. Most patients with primary brain tumors have seen their general practitioner (GP) before being diagnosed, frequently multiple times yet and more than 50% of them are diagnosed of brain tumor by accident or through emergency services. This makes early diagnosis extremely challenging [323].

Misdiagnosis of brain tumors is most common because a doctor may not order additional testing based on a patient's symptoms. Because the symptoms of brain tumors often resemble those of other common diseases, a doctor may diagnose and treat another condition [324]. Although some patients present with headaches or major seizures, the majority experience subtle, intermittent, and multiple changes in their cognitive functioning, sleep, and other "head feelings" for many months, suggesting possible missed diagnostic opportunities [325]

In a study, the data they collected showed 59% of patients correctly diagnosed, 82% of those misdiagnosed had no prior history of cancer. Glioblastoma Multiforme was more common in patients who were initially misdiagnosed than in those who were correctly diagnosed. An important aspect of the diagnostic process is still distinguishing between the acute presentation of a brain tumor and a stroke [326].

Our brain is the one of the delicate and most important control centers for our body. It can be difficult to treat brain tumors effectively. The brain and spinal cord are typically shielded from harmful chemicals by the blood-brain barrier in the body. Numerous forms of chemotherapy

are also prevented by this barrier. If the tumor is close to a delicate part of the brain or spinal cord, surgery may be difficult [327].

In Bangladesh, the scientific database present for brain tumor occurrences on is very limited and insufficient which makes it hard to estimate increases in this incidence. Even with the limited amount of information available, brain tumor incidences have been seen to increase every year [304]. Because of the lack in diagnostic facilities available that cater people living in every part of Bangladesh, obliviousness, expensive treatment; primary care, and routine follow-up facilities are only available to one third of cancer patients. There are 19 medical schools and centers solely devoted to diagnosis and treatment; that is solely deficient for a nation having more than 180 million individuals [328].

Bangladesh has several private and government hospitals offering range of diagnostics and treatment for brain tumors and neurosurgeons performing neurosurgery and other types of treatments. Even clinics offering rehabilitation after surgery or as treatment are increasing with time. The social presence of these hospitals and clinics are very limited. As it is a digital era now, the social presence with vital information like services provided, price list and contact numbers must be available online for the public to access it.

13.2 Future direction

Various common risk factors for brain tumors have been discussed in this review. Although it is challenging to identify risk factors for these tumors because of their rarity, multi-institutional collaborations can make use of numerous existing datasets to advance research. Numerous establishments are proceeding to foster enormous clinical data sets including pre-symptomatic risk factor information, and improvements in molecular characterization of cancer subtypes continue to allow for further investigation of more such factors which are still unknown [315].

One possible way to reduce ionizing radiation as a risk factor would be to reduce the risk of radiation-induced tumors in the future. To achieve this, it is necessary to practice using the lowest radiation dose possible to achieve adequate diagnostic objectives [134].

Targeted drugs could be the future breakthrough for brain tumor treatment. They reactivate silent tumor suppressor genes may activate unwanted oncogenes [151]. Epigenetic studies are currently being conducted to identify new biomarkers, new targets for therapeutic regimens, and to better understand glioma biology [152].

Brain tumors commonly develop quickly and attack healthy brain structures which makes them life-threatening. Brain tumors can both be cancerous and non-cancerous, but even the non-cancerous tumors can be lethal depending on their location in the brain. Patients' chances of survival are reduced when brain tumors are incorrectly diagnosed and treated. Brain tumors can be fatal and early diagnosis would help decrease death rate by it every year. For patients with brain tumors, accurate early medical diagnoses are essential for beginning treatment plans that increase survival rates [329]. Prevention is always better than cure.

The incidence of brain tumor is still unrecognized due to the shortages in data and awareness [330]. Education on the occurrence of different types of brain tumor and how it can be prevented is necessary. Awareness buildup and media campaign can help alert public about this matter. Training of general physicians on cancer warning signs is also necessary along with the setup of early detection centers at each medical college at district levels.

Studies can be done to gain a better understanding of similarities and differences in tumorigenesis, malignant transformation, tumor types and response to conventional therapies and early diagnosis. In turn, much more can be done on this field in terms of studying about how the diagnosis or treatment sectors could be improved in Bangladesh as a whole.

Comparing the epidemiological factor, based on the six different divisions of Bangladesh, research work can be done to understand trends in occurrence and improvement in diagnostics.

Chapter 14

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