Biochemical and genetic markers in neurological trauma and tumors: Review article

Abstract: CNS traumas, and tumors are major health problems. They lead to serious health and economic burdens. They are major causes of disability, or death all over the world. Nowadays, the order of causes of trauma-related death has beenchanged from multiorgan affection to CNStrauma.Assessment of severity and predicting the outcome in a patient with a head, or spinal cord injury, is a must. Most of severity assessment scales depend on the clinical data of the patient. Using of biochemical, and genetic markers that have correlations with severity and outcome in CNS trauma is necessary ofand helpful in clinical field. Ubiquitin C-terminal hydrolase-L1 is an enzyme that is present in the cytoplasmof neurons, and formsabout to 1–2% fromthe proteins foundwithin the human brain, and it is supposed to be a promising biomarker in neurological diseases especially trauma.Neuroglobin (Ngb), is a proteinwhich is distributed mainly in central and peripheral nervous systems, and it has neuroprotective effects against oxidative stress. It is an important biomarker in neurological trauma and tumors.CNS tumors have psychological burden beside their health and economic effects as they may affect personality and both physical and cognitive independence.Various types of mutations have a role in pathogenesis of CNS tumors. Isocitrate dehydrogenase enzyme isoform 1 (IDH1) mutations are frequently identified in primary CNS tumors.Aim of this review: is to give an overview about neurological trauma and tumors as being major health problems, and to spot light on biochemical and genetic markers of promising role as regard pathogenesis, diagnosis, or prognosisof such disorders, with more details aboutUCHL-1, Ngb, andIDH1.
Keywords: CNS trauma; CNS tumors; UCHL-1; Ngb; IDH1.

1.INTRODUCTION

Traumatic brain injury (TBI) is responsible for about one-third of all trauma-related mortalities in the USA annually, and it is a major public health problem in Egypt[1].Traumatic injuries are considered the leading cause of death in people under the age of 46 years[2]. One of the main problems with a head, or spinal cord injury, is assessing the severity. Neuronal damage markers, released in the blood or cerebrospinal fluid (CSF), may provide valuable information about diagnosis and prognosis of these conditions. Protein degradation in secondary brain injury was said to be mediated by ubiquitin, in which ubiquitin C-terminal hydrolaseL1 (UCHL-1) concentrated in neuronal cells, and it is supposed to be a promising biomarker in neuropathology [3].Neuroglobin (NGB) is a protein monomer that is structurally related to myoglobin, and it has many important functions in protecting the neurons from oxidative hazards[4].Neuroglobin (Ngb) is responsible for enhancing oxygen transportation through blood-brain barriers, as well as increasing the availability of oxygen in mitochondria. Neuroglobin is responsible for detecting cellular oxygen concentrations like a sensor, and is involved in the detoxification of harmful reactive oxygen, so it supports neuron survival in hypoxic and ischemic conditions. as well

as enhancing cell viability within active cells[5].CNS tumors can lead to severe disability,
in the form of seizures, poor memory or speech problems, as well as physical dysfunction[6].
Accumulation of multiple genetic and epigenetic alterations in genes and signaling pathways, such as isocitrate dehydrogenase enzyme isoform 1 (IDH1) mutations, is an important cause of CNS neoplastic transformation[7].

2.CNS traumas

2.1.Traumatic brain injuries(TBIs)

2.1 1 Definition

A clear, concise definition of traumatic brain injury (TBI) is essential for reporting,comparison, and interpretation of studies on TBI. Traumatic brain injury was defined by, The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health, as an alteration in brain function, or other evidence of brain pathology, caused by an external force[8].

2.1 2 Causes

Many causes can lead to occurrence of traumatic brain injury such as: motor vehicle accidents, falls, blunt trauma[9]. Among all these causes, a motor vehicle accident is considered the leading cause of brain trauma or brain injuries [10].

2.1 3 Epidemiology, and socioeconomic effects

The mean value of the number of hospitalized patients with fatal TBI in Europe was 235 per 100,000 while in the US this value was doubled [11]. About 50,000 deaths related to TBI occur in the US per year, and 1.4 million TBIs occur globally with a coast of about 60 billion dollars annually. In the Kingdom of Saudi Arabia, an 8-year retrospective study reported 1,219 patients below the age of 18 years to be diagnosed with TBI [10].

2. 1 4 Classification

There are many methods to classify head injuries: according to mechanism of trauma (closed or penetrating injury), morphology (fractures, focal intracranial injury, diffuse intracranial injury), or severity of injury (mild, moderate, or severe).Primary brain injury means the immediate brain damage due to trauma e.g., cerebral contusions,shearing lesions, lacerations, and acutesubdural or epidural hematomas. Secondary brain injury refers to progressive cerebral oedema, ischemia, and the expansion of cerebral contusions and the surrounding focal oedema, which lead to increase in intracranial pressure(ICP) within the confined skull and can eventually cause cerebral herniation and death [12].In the Glasgow Coma Scale (GCS) system, the patients with head injury would be classified into three groups: mild, moderate, or severe. Patients with mild injury have GCS scores from 13 to 15. Those with moderate injury have GCS scores from 9 to 12 and the patients with severe injury have GCS scores which are less than 8[9].Head Injury Severity Scale (HISS) is a five-interval severity scale (minimal through critical)

based primarilyon initial GCS score. The HISS scale also includes the aspects of retrograde amnesia, loss of consciousness (LOC), and focal neurological deficits for each severity intervals[13].Then in 2000, HISS classification was modified, by the Scandinavian Neurotrauma Committee (SNC) by classifying head injuries into minimal, mild, moderate, and severe.Minimal head injury is presented by a patient with GCS 15 at admission and with no LOC or focal neurological deficits.Mild head injury is defined as initial GCS of 14–15, brief LOC (<5 min) and no focal neurological deficits.Moderate head injury defines a patient with initial GCS of 9–13 and/or focal neurological deficits or LOC ≥ 5 min after head trauma.Severe head injury includes all patients with an initial GCS score of 8 or below, hence, unconscious patients[14].The Revised Trauma Score (RTS) is a numeric grading system for estimating the severity of injury. Its parameters include the GCS, systolic blood pressure, and respiratory rate, each giving rise to a score between 0 and 4. The degree of injury severity can be estimated by the total sum of these three parameters, with the highest score is 12, which represents the least severe injury[12]. TheGlasgow Outcome Scale-Extended (GOSE) has become one of the most widely used scales for assessment of the outcome after traumatic brain injury as regard global disability and recovery[15].The Disability Rating Scale (DRS) is a short, efficient, and rapid method for assessing levels of functional disability for traumatic brain injury (TBI) patients [16]. The DRS is an 8-item measure (each rated on a 3–5-point scale) that is summed to give a total score[17].

2.2.Traumatic spinal cord injury (TSCI)

2. 2 1 Effects

Traumatic spinal cord injury (TSCI) is a high disabling injury; it can lead to manycomplications such as: damage or loss of sensation and motor function, dysfunction of bladder or bowel and also may lead to multiple organ dysfunction[18].

2.2 2 causes

There are many causes of SCI, including falls (falls from height, simple falls), motor vehicle accidents (MVAs)/motor vehicle crashes, sports-related accidents, violence and other remaining causes of injury. Motor vehicle accidents (MVAs) and falls are the most common causes of injury accounting for nearly equal percentages[19].

2.2 3 Epidemiology

As a result of the expansion of human activities, the incidence of SCI also increased gradually over last years. The incidence varied from 13.019 per million to 163.420 per million people. The cervical level of spine is the most common affected site. Incomplete cord injury is more common than complete injuryquadriplegia is more common than paraplegia.Estimationsof SCI mortality among developed countries varied from 3.1%to 22.2%, while mortality in non-developed countries ranged from 1.4% to 20.0%[18].

2.2 4 Classification according to severity

The extent of injury is defined by the American Spinal Injury Association (ASIA) Impairment Scale using the following categories:

- A = Complete: No sensory or motor function is preserved in sacral segments S4-S5
- B = Incomplete: Sensory, but not motor, function is preserved below the neurologic level and extends through sacral segments S4-S5
- C = Incomplete: Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have a muscle grade of less than 3
- D = Incomplete: Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have amuscle grade that is greater than or equal to 3
- E = Normal: Sensory and motor functions are normal[20].

2.3. CNS tumors

2.3 1 Epidemiology, and burdens

CNS tumors are relatively rare, but they represent a significant cause of cancer-related morbidity and mortality especially among children and young adults where they respectively account for approximately 30% and 20% of cancer deaths[21].Primary CNScancers can occur at any age and in any site within the central nervous system, but mostly (more than 90%) affect the brain. These types of cancerare major causes of disability and deathin all populations[22]. The global incidence of neurological tumors in 2016, was 330 000 patients while 227000persons died due to the disease. East Asia was the region with the most incident cases of CNS cancer for both sexes in 2016, followed by western Europe, and south Asia. The top three countries with the highest number of incident cases were China, the United States of America (USA), and India[23].

2.3 2 Risk factors

There is not any biological, environmental, or social causes that identified to leadto CNS tumors except ionizing irradiation whether as a therapy, or during wars[21].

2.3 3 Types, and grading

Glioma, with its different types, is considered the most abundant histopathological varietyof1ry neurologicaltumors. Others are medulloblastoma, meningioma, glial tumors(e.g., ependymoma, and schwannoma), and finally lymphoma of the CNS[24]. Glioblastoma, which represents the most frequentglial tumor inthe brain, often cause death during 24months afterbeing diagnosedeven ifall treatment lines were taken[25].The most common histological types in children involve medulloblastoma, astrocytoma, tumors of germ-cell origin,gliomas of the brainstem,and ependymomas. Good prognosis and increased life expectancyis common in children affected by these types of tumors in presence of comprehensive treatmentstrategies[26].
Dividingneurological tumors into different gradesrelies onfour features in the morphology: presence of

atypicalcells, mitotically active cells, necrotic changes, and presence of microvascular proliferation. IN the light ofthesefeatures mentioned, CNS tumors are graded into:

- Grade I: in which tumor tissueshaveno of the mentioned features. This category is characterized by increasing in size slowly, being benign, and increased life expectancy.
- Grade II: possess one feature only,such as, atypical cells. Neoplasms of this groupincrease in size slowly, meanwhile, theyhave a high recurrence rate, also,could be benign or non-benign.
- Grade III: possess 2 features, such as, atypical cells which are mitotically active.Neoplasmsof this group are malignant and mostly have a high recurrence rateas neoplasms with higher grades.
- Grade IV: possess 3 or 4of the features mentioned before.Neoplasms of this group are not benign at allhaving a high aggressiveness[27].

3.Ubiquitin c-terminal hydrolase L1(UCHL1)

3.1. The ubiquitin system: mechanism of action, and function

Ubiquitin is a protein formed of seventysix building units, i.e., amino acids linked to each other via peptide linkages. It could be attachedto sites in a certain polypeptide, as a single ubiquitin molecule or as ubiquitin polymers,as a post-translational modification. The most common ubiquitinated amino acid is lysine (Lys), however the side chains containing hydroxy amino acids threonine, and/or serine, or the Sulphur-containing cysteine, and also the amino group at the amino end of the polypeptide chain, could be changed[28].Ubiquitin can be insertedinto target proteins via a covalent bond between the ε-amino group of the Lys residue of the protein and the last carboxylate group of the terminal glycine (Gly76) of Ub through an isopeptide bond. This covalent addition is catalyzed by three enzymes that act in in a sequential order. They are known as the E1 Ub activating enzyme, E2 Ub conjugating enzyme, and E3 Ub ligases in an ATP-dependent process.Ubiquitin can be removed from proteins or from polyubiquitin chains through hydrolysis by one of deubiquitinases (DUBs). There are about 100 DUBs in humans, most of them are cysteine proteases, except the JAMM proteases, which needs Zn dependent catalysis. The cysteine protease DUBs are subdivided into six groups: the Ubiquitin Specific Proteases (USP), Ubiquitin C-terminal Hydrolase (UCH), Machado-Josephin Domain, Ovarian Tumor Proteases, and the more recently discovered Mindy and ZUFSP groups[29]. Besides L1 subtype of ubiquitin carboxylic end hydrolyzing enzymes (UCH-L1), the class of UCH has many other members named as, breast cancer type 1 (BRCA 1) susceptibility protein, L3 subtype of ubiquitin carboxylic end hydrolyzing enzymes, and finally L5 subtype; nevertheless, exclusively UCH-L1 is prevalent in the brain tissue [30].Ubiquitin-proteasome system through its role in protein degradation, is essentialfor many different cellular

processes, such as response to stress, cell differentiation, and transmission of cellular information. L1 subtype of ubiquitin carboxylic end hydrolyzing enzymes; UCH-L1, is special in that it engages in a variety of functions, it has a ligation and hydrolyzing abilities. Via acting in hydrolysis, UCHL1 can participate in recycling and removing ubiquitin molecules out of damaged protein particles, and viaits ligation capability, it binds ubiquitin particles to each other, then it can be utilized to tag certain proteins. to be hydrolyzed later on. UCHL1 key functions include regulating cellular ubiquitin and glutathione levels, and regulatingcell cycle[31].During both physiological and neuropathologicalsituations, UCH-L1 regulates brain protein metabolic processes by directing the proteasome system, taking part in eliminatingproteins present in concentrations higher than needed, abnormally folded proteins, orproteins affected by oxidation[30].UCHL1 is required for appropriate motor function and is thought to play a role in memory function. UCHL1 is also found in the peripheral nervous system, such as the dorsal root ganglion and trigeminal ganglion neurons. It interacts with proteins in the neuronal cytoskeleton and is essential for axonal integrity and transport. Furthermore, because it is a component of the axonal skeleton, UCH-L1 plays a function in axonal transport. UCHL1 is highly expressed in testes, carcinomas of lung, prostate, large intestine, kidneys,mesenchyme, pancreatic tissue, breast, in addition to the nervous system[31].

3.2. Structure of Ubiquitin C-terminal Hydrolase L1 (UCH- L1)

Jackson and his colleagues, were pioneers in identifying UCH-L1 as a protein present specifically in brains of human beings. They mentioned that such protein had a molecular mass about twenty-seven kilo Daltons. They made this great discovery utilizing two-dimensional polyacrylamide gel electrophoresis of a high resolution in the early 1980s [32].The deubiquitinase enzyme UCH-L1, is a globular protein containing a peptidase C12 superfamily catalytic domain with very short N- and C terminal extensions. There are five crossings of the peptidase C12 polypeptide backbone forming ‘Gordian’ knot. In the final 3D structure,there is a densely compacted hydrophobic center of β- segments surrounded by 2 lobes of α-helical structures.This knotted backboneprotects UCH class DUBs from undesired proteasomal unfolding and degradation.Once UCH-L1 binds to ubiquitin, it undergoes morphological rearrangementthatbrings histidine, aspartate, and cysteineamino acids that are present inside the catalytic site for protein degradation nearer together, promoting enzyme being activated [28]. Products of abnormal oxidation of lipid,mutagenesis of gens, and modifications pf protein structure after being translated, can all affect the structure and function of UCH-L1 [33].Overexpression and/or mutation of UCH-L1 gene has been linked to various cancers and neurodegenerative diseases[34].

3.3. Biological roles of UCHL-1 in the CNS

3.3.1Antioxidant function of UCHL-1 in neurons

It has been proposed that UCH-L1 has a neuronal antioxidant function because the presence of insoluble or misfolded UCH-L1has been approved in many neurodegenerative disorders[34].One hypothesis supporting this idea is that the conserved Cys152 residue acts as a redox buffer and reacts with, and chelates, free radicals in neurons[35].

3.3.2Ubiquitin C-terminal Hydrolase L1 (UCH-L1) in CNS trauma and neuronal injury

Ubiquitin-proteasome system plays a major role in repairing injured axons and neurons through its function in removing abnormal proteins. After brief ischemia, this is critical because abnormal ubiquitin proteins accumulate within neuronal tissues, leading to cell death. UCHL1 is important for maintaining axonal integrity and axonal transport. Synapses are also regulated by UCHl1. Axon pathology and significant abnormalities in motor functions are caused by UCHL1 mutations [31].The blood biochemical marker, UCHL1 has now been approved as a tool for assessing and classifying severe head injuries due to trauma. Ubiquitin C-terminal hydrolase-L1 (UCHL1) levels were calculated in sera and cerebrospinal fluid samplesfrom patientswho suffered fromhead trauma affecting the brain, and put in comparison with non-traumatized controls in many clinical trials. These investigations found a considerable elevation in the measured concentrations of L1 subtype of ubiquitin carboxylic end hydrolases in the acute phase (throughouttwenty-four hours after trauma) and a link was found between the measured levels and the degree of the damage of brain tissue. Also, studies on rat models of TBI revealed that the protein's expression has increased[30].

3.3.3 Role of Ubiquitin C-terminal Hydrolase L1 (UCH- L1), incancer development

UCHL1 amounts that are excessive are implicated in the development of malignancy. UCHL1 actionin cancer had been connected with its role in cell cycle control, perhaps via affecting the p53 tumor suppressor protein, β -catenin, as well as signal transmission Akt pathways.Because of its hydrolytic capacity, UCHL1 stimulates Akt-mediated transmission of signals, which in turn encourages cell motility, infiltration, and multiplication. Expression ofUCHL1 gene can happen in cancereven in unexpected sites where it is usually not expressed under normal conditions, such as breast, colorectal and pancreatic cancers. In contrast to prior findings, other scientists concluded that deubiquitinase, UCTL1, induced halt of cell-division cycle and suppressed tumor progression in liver, mammary glands, and ovarian malignancies [31].Increased amounts of UCHL1 in neuroblastomas were associated to being well-differentiated, which according to Gu and his colleagues, can be considered as a sign of favorable prognosis [36].

3.3.4Ubiquitin C-terminal Hydrolase L1 (UCH- L1), and neurodegeneration

Presence of ubiquitinated protein aggregates is a common hallmark in many neurodegenerative disorders, likeparkinsonism, and Alzheimer's disease (AD). These pathologies have

been related greatly to abnormalities of UCHL1 gene. UCHL1 is present in bodies of Lewy and neurofibrillary tangles. The activity of UCHL1 is suppressed by ROS generation, which has an impact on the normal neuronal biological activities. UCHL1 amountwas shown to be lower in neurodegenerative illnesses like amyotrophic lateral sclerosis, and AD [37].

3.4. Other roles of UCHL1 in different tissues

3.4 .1 Role of Ubiquitin C-terminal Hydrolase L1 (UCH- L1), in spermatogenesis

System of Ubiquitin manipulationproteosomalnetwork plays a role in all different stages of spermatogenesis, so disturbances of its balance can lead to many abnormalities. UCHL1 has a diverse action during spermatogenesis; It participates in the activation of germ cell death and also regulates anti-apoptotic factors during spermatogenesis. Increased levels of UCHL1 are linked to a higher rate of germ cell death, most likely due to removal of ubiquitin residues from p53 leading to increased activity of apoptosisthrough the mitochondrial pathway[38].

3.4 2 Ubiquitin C-terminal Hydrolase L1 (UCH- L1), and angiogenesis

UCHL1 mediates vascular remodeling and has a role in angiogenesis in endothelial cells through increasing the expression of eNOS (endothelial nitric oxide synthase), and inhibiting NF-k (Nuclear factor k) activity mediated by TNF (Tumor Necrosis Factor), which may improve ischemic vascular diseases. UCH-L1 also promotes tubule development in vitro and blood vasculature formation in vivo [31].

3.4 3 Ubiquitin C-terminal Hydrolase L1 (UCH- L1), and inflammation

Following stimulation with proinflammatory cytokines IFN- and TNF-', UCHL1 was found to be increased in multipotent mesenchymal stromal cells (MSCs).In patients with acute appendicitis, the amount of UCHL1 in the plasma was highest before the surgical procedure and gradually reduced afterward. The metabolic response to inflammation may be reflected in UCHL1 levels. [39].

3.4 4 Ubiquitin C-terminal Hydrolase L1 (UCH- L1), and skeletal muscle cell differentiation and proliferation

Animal studies revealed that UCHL1 is primarily expressed in type I muscle fibers, and it has a role in slow twitch muscle growth and function which are regulated through its action. In vivo and in vitro, deletion of UCHL1 resulted in muscular hypertrophy. [40].

3.5. Human UCHL-1 mutation

A missense mutation due to glutamate-alanine substitution at position 7inside ubiquitin c terminal hydrolase L1 poly peptidehas been identified as a reason for of juvenile onset neurodegenerative pathology in three childrenwho were apparentlyhealthyduring infancy but then get blind just at age of five and experienced also, incoordination of movement in a progressive manner, upper motor neuron disorder, involuntary abnormal eye movements, dorsal column dysfunction, rigidity. No

other manifestations were seen outside of the nervous system[41].The Glu7 residue in UCH-L1 is needed for ubiquitin binding. Ataxic pattern seen in people with a UCH-L1, which is defective in ligation/hydrolyzing abilities, shows that the neuronal atrophy seen in rodent models is most likely linked to lack of that kind of activity[31].Mice lacking the UCHL1 gene had gradual motor disability as well as anomalies in the synaptic connections of corticospinal neurons[42].

4. Neuroglobin (Ngb)

4.1. Overview

Globins are heme-containing proteins that can be found in all living beings of the animal kingdom. They play a crucial function in the creation of oxidative energy [43].Over many decades, hemoglobin, and myoglobin had been known as the only globins present in vertebrates. But in 2000, a third globin type was discovered by mining the genome sequence data. Based on a preferential expression in the nervous system, this globin was referred to as neuroglobin[44].Neuroglobin (NGB) is a protein which is structurally related to myoglobin and plays a crucial redox-dependent defensive function in neurons[45]. Ngb is a monomer formed of 150 amino acid residues and weights 17 kDa and its expression is induced mainly by hypoxia such as in case of decreased cerebral or spinal blood supply. It has different concentrations according to the tissue. For example, Ngb concentrations in rods and cones of the retina can be up to 100 times higher than in neuronal cells of the nervous system because they have a high need for oxygen[46].

Cytoglobin, globin X, which is seen in some murine and amphibian creatures,and globin E, which is present in bird eyeballs, allare different types of the globin family [47]. The last globin found, cytoglobin (Cgb), has 190 amino acids arranged in two chains in a dimeric configuration. It can be present in the heart, lungs, liver, and stomach, and among other organs [46].

4.2. Neuroglobin structure

Globins are globular metalloproteins that have a common tertiary structure characterized by six or four α-helices (3/3 or 2/2-fold symmetry, respectively) that make a sandwich around a heme group. They bind O2 in a reversible manner via an iron-containing porphyrin ring. Neuroglobin (Ngb) has the same common globin structure consisting of eight α-helices denoted A–H, with the heme prosthetic group located between helices E and F. But it differs in structure from hemoglobin and myoglobin as the heme iron (heme-Fe) of Hb and Mb proteins is pentacoordinated, but iron present inside heme structure of neuroglobin is coordinated hexagonally through 4 nitrogen atoms present in the pyrrole ring within the plane of heme, and the far histidine (E7)64 side chain, and the near histidine(F8)96 amino acid particles [43].

4.3. Neuroglobin functions

Neuroglobin (Ngb) is responsible for increasing oxygen transportation through blood-brain barrier (BBB), as well as increasing the availability of oxygen in mitochondria. Neuroglobin actsas a sensor that detects cellular oxygen concentrations, and is involved in the detoxification of harmful reactive oxygen, so it supports neuron survival in hypoxic and ischemic conditions. as well as enhancing cell viability within active cells.Ngb could play a role in signaling pathways by preventing the separation of guanosine diphosphate from G protein α, for example. Neuroglobin could be involved in a redox pathway which, prevents programmed cell death by lowering cytochrome c levels [44].It's also been postulated that Ngb's neuroprotective characteristicsare linked to its ability to interact with mitochondrial cytochrome C (Cyc), rather than onlyits free radical scavenging ability.[48].

4.4. Role of Ngb in protection against ROS, and NOS

Not only Hb(II)-O2 and Mb(II)-O2 have the ability of rapid reaction with nitric oxide (NO) to produce nitrate and Hb(III) or Mb(III) but also human Ngb(II)-O2 can play this scavenging role. Human Ngb(II)-O2 reaction with NO is very rapid and proceeds *via* a peroxynitrite intermediate which bounds transiently to Ngb(III) [49]. Neuroglobin is expected to play a same function asmyoglobin, acting as a nitric oxide-dioxygenase when oxygen tension is decreased and nitric oxideconcentrations are elevated as seen during ischemia. Therefore, Ngb can either breakdown or generate NO, according to oxygen tension, and that might be important in the modulation of vascular tone, as regard contraction and relaxation, and in controlling the level of mitochondrial respiration [50]. Mitochondria might create a lot of damaging oxygen free radicals as a consequence of enhanced oxygen utilization. Whenever the availability of oxygen is reduced, this phenomenon will be most evident. Globins are suggested to have the ability to protect the cells from ROS stress and Ngb can play an identical role inside neurons [44].

4.5.Neuroprotective properties of neuroglobin

Neuronal tissue is extremely vulnerable to hypoxia-induced stress. Following ischemia-related strain, every molecule which possess the ability to increase oxygen delivery or reduce reactive oxygen species -induced damage is supposed to improve cell survival. In agreement with this, many studies have shown that lowered Ngb amounts in experimental models hindered viability of cultured neuronal cells, whilst amplification of Ngb increased vitality. [51,52].

Ngb is linked to microdomains of lipid rafts and α-subunits of heterotrimeric protein G and can be activated during oxidative stress, with structural changes that lead to neuroprotection. Moreover,

Ngb, which is present in the mitochondria, reacts with the voltage-dependent anion channel (VDAC) and cytochrome c, which illustratesthe function it does in protecting nerve cells on the mitochondrial level [53]. It has been shown that Ngb reduced amyloid-β (Aβ) protein toxicity in mouse neurons and pheochromocytoma cell lines suggesting that its antioxidant properties could protect against AD. Many experiments, carried out on AD patients' brains after death, revealed thatthroughout initial and intermediate disease stages, neuroglobin protein synthesis in hippocampal region was enhanced, but Ngb concentrations fell to control levels in late AD[43]. In another research, it was hypothesized that The activation of Ngb via the PI3K/AKt pathway reduces caspase action, allowing cells to survive, which could be an alternate technique for preventing AD progression [54]. Other studies have shown that neuroglobin reacts very rapidly with cytochrome *c* released from mitochondria during cell death, thus interfering with the intrinsic pathway of apoptosis [55].The potential neuroprotective function of Ngb has been also investigated in Huntington's disease (HD) [43]

4.6. Neuroglobin and CNS trauma

Basic pathologic criteria of TBI include bleeding, cell death, increased production of β-amyloid, basic fibroblast growth factor (FGF-2), and over expression of Ngb that remains upregulated until the sixth day post-injury. Neuroglobin expression is increased also in case of decreased oxygen, or blood flow to the brain[56].During an experimental simulation of trauma induced injury within the brain, increased neuroglobin expression was associated with noticeabledecreaseof motor and somatosensory impairments when put in comparison to controls that did not overexpress neuroglobin[57].On the other hand, measurement of Ng levels in patients with traumatic brain injury revealed a time-dependent increase of neuroglobin levels in serum of patients with TBI within the 96 h post-injury also it was observed that upregulation of neuroglobin correlated to severity and prognosis of TBI as serum NG levels significantly increased in TBI patients with bad outcomes [58].

As regard spinal cord trauma many studies showed that over expression of neuroglobin is associated with good recovery from the spinal cord injury. Overexpressing Ngb improved the recovery of locomotor function after spinal cord injury significantly. Such effect may be due to the inhibition of neural apoptosis through the mitochondrial pathway[59].

4.7. Neuroglobin and CNS tumors

Cancer is associated with increased oxidative stress due to continuous cell division and increased cellular metabolic reactions. But on the other hand, cancer cells more internal protective

mechanisms against oxidative damage when compared to the normal cells so, they are able to withstand apoptosis. Discovery of viability - enhancing elements and adaptation programs in malignanttumors that protect them from ROS generation opens up a plethora of potential therapies for cancer treatment. Neuroglobin has been proposed as a novel cancer related molecule since it is an oxidative stress detector and it can also protect cells from redox dysregulation [60]. Different researchers studied the transcription, and translation of neuroglobin gene human beings in case of occurrence of neoplasms of the brain or spinal cord. They found that NGB expressions was more in astrocytoma cell linesfrom both mouse and the human origin and in neuronal tissues from patients with astrocytoma whencompared to normal brain or spinal cord cells, implying that neuroglobin may play a function in astrocytoma cellular response to hypoxia and situations of increased burden of oxidation [61].Furthermore, a comparison of NGB mRNA and protein expression inside cells of glioma tissue samples with those levels into healthy neuronal cells, revealed augmentation of NGB levels in glioma cells. There had been a link connecting NGB expression and worse prognostic features of glioma as regard tumor grading, as well as, significantlydecreased expectedlifespan, leading to the recommendation of NGB use in expecting prognosis of people with glioma [60].

5. Isocitrate dehydrogenase I (IDH1)

5.1. Overview

It is known that, the tricarboxylic acid (TCA) cycle (namedby the citric acid cycle or Krebs cycle also), is used by all aerobic organisms to produce adenosine triphosphate (ATP) from acetyl-CoA obtained from carbs, lipids, and proteins through. The TCA cycle also produces intermediate products that can be employed in denovo protein, lipid, and nucleic acid synthesis [62].Isocitrate dehydrogenases (IDHs) catalyze the oxidation-decarboxylation of isocitrate (ICT) into -ketoglutarate (-KG) utilizing NAD or NADP as a cofactor, which is one of a series of metabolic events in the TCA cycle. NADP-dependent cytoplasmic IDHs are found in most prokaryotes (NADP-IDHs). NADP-IDHs and NAD-dependent IDHs both exist in Eukaryotes (NAD-IDHs).Two types of NADP-IDHs are found in the cytoplasm and mitochondria of human and other mammalian cells, and one NAD-IDH is found in the mitochondria. HsIDH1, HsIDH2, and HsIDH3 are the human NADP-IDHs and NAD-IDHs, respectively [63]. While all the three types of IDH catalyze similar enzymatic reactions, they have different cellular functions and localization. IDH1 and IDH2 exist as homodimers which reduce NADP+, while IDH3 is a structurally distinct enzyme which

utilizes NAD+ as a cofactor. IDH2 and IDH3 are mitochondrial enzymes which play critical roles in generating mitochondrial NADPH and driving TCA cycle flux, respectively. In contrast, IDH1 is localized primarily in the cytosol where it plays an important role in maintaining cytosolic NADPH levels [64]. HsIDH3 is recognized to play a catalytic role in the citric acid cycle, whilst HsIDH1 and HsIDH2 play a pivotal role in cellular protection from oxidative stress hazards, oxygen free radicals' elimination, lipogenesis and cholesterol synthesis. The development of a variety of metabolic disorders and malignant tumors has been linked to abnormal activities of all these three enzymes.[63].

5.2. Structure, and regulation of IDHs

5.2. 1 NADP-IDHs

NADP-IDHs are found in both prokaryotes and eukaryotes and function as homodimers with catalytic activity in both subunits. The catalytic mechanisms of these enzymes are similar, but differ in regulationof catalytic processes[65]. Prokaryotic and eukaryotic Kinases and phosphatases regulate critical signal transduction in cells by reversibly phosphorylating and dephosphorylating proteins. They predominantly act on hydroxy amino acids tyrosine, threonine, serine particles of proteins [66].

Isocitrate dehydrogenase kinase/phosphatase (AceK) is a peculiar bi-functional enzyme in Escherichia coli that functions as both a protein kinase and phosphatase. AceK responds to dietary diversity by addition or removal of phosphate to / from isocitrate dehydrogenase (IDH)[67].The reversible phosphorylation results IDH, which governs the junction in-between the Krebs and the glyoxylate bypass cycles, canlose its activity or become activated by addition of phosphate reversibly. Furthermore, as compared to its kinase and phosphatase actions, AceK has an exceptionally robust ATPase function[68].The double functioning kinase/phosphatase AceK controls NADP-IDH activity by reversibly phosphorylating and dephosphorylating a strictly defined Ser in the catalytic site, and other bacterial NADP-IDHs may have the same regulatory mechanism[63].The performance of human IDH1 is controlled by a morphological shift in a critical structural component in the catalytic site triggered by substrate binding, and perhaps other mammalian NADP-IDHs may use an analogous regulatory mechanism[69].

5.2. 2 NAD-IDHs

- **Prokaryotic NAD-IDHs**

Saccharomyces cerevisiae is a kind of yeast which harborProkaryotic NAD-IDHs. The ScIDH1/ScIDH2 heterodimer is the basic functional unit of NAD-IDH, which is made up of a regulatory subunit ScIDH1 and a catalytic subunit ScIDH2.The mature polypeptides are similar in size (349 and 354 amino acid

residues, respectively) and share 42% residue sequence identity. Both subunits are essential for holoenzyme structure and function [70], and the heterodimerthen eventually becomes a heterotetramer and then a heterooctamer [71]. The active site is in ScIDH2, while the allosteric site is in ScIDH1. IDH2 has a catalytic isocitrate/Mg2+ and NAD+-binding site, whereas IDH1's homologous region is involved in collaborative isocitrate engagement as well as the allosteric activator AMP binding. When citrate (CIT) and AMP which areenzyme activators bind to the allosteric site, the active site undergoes conformational changes at the heterodimer interface, resulting in inducing enzyme activity [72].

- **Eukaryotic NAD-IDHs**

In general, NAD-IDH of mammals, has a more complicated structure and regulatory mechanisms than prokaryotic NAD-IDH. NAD-IDH in mammals is made up of 3 sorts of subunits in a 2α:1β:1γ ratio. The mammalian α subunit is similar in structure to the fungal IDH2 subunit, implying that it acts a enzymatic activity, whilst the and components are structurally similar to the yeast IDH1 subunit, implying that it responsible for regulating enzyme activity [73].Alpha, Beta, and Jama domains haveapproximately 37, 39, and 39 kilo Daltons, respective weights. Nearly 40% sequential identity exists between the alpha and beta components, whileα, and γ components around 42 percent structuralsimilarity, whereas β, and γ components have approximately 52 percent structural similarity. Alpha andbeta subunits build the (αβ) heterodimeric structure, and also the α and γ subunits create a second (αγ) dimer, and finally these 2 heterodimers are joined into a 2(α2βγ)tetrameric structure and then into a (α2βγ)2 heterooctamer [63].As it stimulates irrevocable most important reactionwhich controls the rate of enzymatic activity in subsequent stages in the Krebs metabolic pathway, it is tightly regulated through substrate availability [citrate, adenosine 5′-diphosphate (ADP), isocitrate (ICT), It is carefully controlled via many mechanisms, such as:

1. + ve feedback exerted by substrate abundance i.e., increased levels of citric acid, ADP, isocitric acid, oxidized NAD+, as well as the cofactors; Mg2+ and Mn2+,
2. -ve feedback effect that occurs when byproduct such as: NADH besides alpha ketoglutarate accumulate,
3. competitive suppression by ATP,

The goal of these regulatory actions is to make a balance between both alpha ketoglutarate, and isocitrate cellular levels. α component of the enzyme is crucial for ICT loading, while β has a structural role by promoting component assembling, but γ component has been engaged in the allosteric mechanism regulating IDH activity mediated by ADP and citrate binding [74].Both αβ and αγ heterodimers'

subunits exhibit catalytic properties; nevertheless, only the γ monomer serves a regulatory action through an allosteric regulation, whilst the β monomer has no regulatory involvement but is necessary for optimum performance. Citrate and adenosine diphosphate both positively regulate the αγ dimer, but NADH has a negative effect. Furthermore, low amounts of ATP can stimulate these enzymes activity whereas large doses of ATP suppress them. The αβ heterodimer activity, on the other hand, is suppressed through both NADH and ATP and cannot be triggered by CIT or ADP[75].

5.3. Physiological metabolic actions of human IDHs

IDH1, IDH2, and IDH3 genes in humans produce 3 variants of the IDH enzyme, all of which do key functions in cell metabolism. IDH1 is present in the matrix of the mitochondria, while IDH2 and IDH3 are distributed in the cytosol and peroxisomal system[76].Despite their differing locations, IDH1 and IDH2 both are isoenzymes that catalyse the transformation of isocitrate to 2-OG with the help of nicotinamide adenine dinucleotide phosphate (NADP+) as a coenzyme, resulting in NADPH as a product. NADPH in the cytosol perform an essential antioxidant function.[77]. One of peroxisomal IDH1 may be to provide cytosolic NADPH for several NADPH dependent enzymes, such as 3-hydroxy-3-methylglutaryl-CoAreductase, acyl-CoA reductase, and 2,4-dienoyl-CoA reductase. The activity of IDH1 is the only known source for peroxisomal NADPH.Another physiological role of peroxisomal IDH1 is to Provide -ketoglutarate, which is required as a cosubstrate for the phytanoyl-CoA-hydroxylase reaction which catalyzes a step in the degradation of phytanoic acid. Several metabolic functions for phytanic acid have been reported such as: white adipocyte differentiation; and activation of uncoupling protein-1 gene transcription and brown adipocyte differentiation [78]. Also, alpha ketoglutarate-dependent dioxygenases use 2-OG as a cofactor. Ten–eleven translocation (TET) enzymes, used in DNA demethylasesation besides Jumonji-C (JmjC) domain-containing enzymes, which act on histone lysine to remove methyle groups, are the most well-known nuclear 2-OG-dependent dioxygenases[76]. dioxygenases of the cytoplasm include the prolyl hydroxylase domain (PHD)- containing enzymes which have roles in many metabolic processes [79].IDH3 catalyzes the production of 2-OG from isocitrate, but with NAD+ as a coenzyme, and creates NADH, which is employed in the electron transport chain to generate adenosine triphosphate (ATP)[76].

5.4. IDH mutations in cancer

Abnormal metabolism of cancer cells often correlates with mutations in genes encoding for metabolic enzymes, including those involved in the tricarboxylic acid (TCA) cycle and

related metabolism. As regard carcinogenesis, the gene coding for IDH1, is by far, the most commonly altered gene of metabolism. Mutant IDH1 and IDH2 genes result in active site replacements in the corresponding enzymes, which have a significant impact on IDH performance, metabolic activity, leading to cancer formation[80]. IDH gene alterations mostly impact the arginine amino acid at position 132 (R132) in IDH1polypeptide chain, the equivalent arginine 172 (R172) residue in IDH2, or the arginine 140 (R140) residue in IDH2, rendering these mutational foci[81].Mutations in the isocitrate dehydrogenase gene IDH1 in cancer were first identified in a whole-exome sequencing study of 22 glioblastomas [82]. Then, it was approved that IDH mutations are prevalent in various types of cancer, including low- grade glioma and secondary glioblastoma (80%), acute myeloid leukaemia (AML; 20%), cholangiocarcinoma (20%), chondrosarcoma (80%), sinonasal undifferentiated carcinoma (49–82%) and angioimmunoblastic T cell lymphoma (32%) [81].IDH's catalytic domain undergoes structural changes as a result of mutations, leading to the catalysis of a partial reverse reaction, in which α-KG is reduced to (R)-2-hydroxyglutarate [(R)-2HG] [74].

High concentrations of D-2HG negatively affect 2OG oxygenases implicated in epigenetic regulatory mechanisms, such as the Jumonji C domain containing histone lysine demethylases (JmjC KDMs) and the ten eleven translocation (TET) oxygenases, which catalyze removal of methyl groups in certain sites of histone and addition of oxygento N-methyl cytosine in DNA[83].D-2HG's via competitively inhibiting JmjCKDMs, as well as, TETs may help increased methylation of chromatin seen in IDH mutant glioma [84]. D-2HG through being a competitive inhibitor toboth JmjC KDMs as well as TETs, may play a role in the histone and DNA modifications in the form of hypermethylation states seen in IDH mutant gliomas [84]. These chromatin modifications are thought to prevent malignant transformed cells from differentiating, allowing them to thrive and replicate, encouraging carcinogenesis. [80].

Table (1) Cellular effects of D-2HG:

Effect of D-2HG	Molecular target	consequences	refrences
inhibition	JmjC KDMs (Jumonji C domain-containing histone lysine demethylase)	Histone methylation, blocked MyoD mediated differentiation, mTOR (the mammalian target of rapamy	Liuet al. [80], Chowdhury et al. [85], Sulkowski et al. [86]

		cin) activation	
inhibition	TETs (ten-eleven translocation oxygenases)	DNA methylation	Liu et al. [80], Yeung et al. [83]
inhibition	PHDs (HIF prolyl hydroxylase domain enzyme)	HIF-1 α (hypoxia-inducible factor-1a) induction	Liu, et al. [80], Sasaki et al. [87]
inhibition	Collagen prolyl and lysine hydroxylase	Impaired collagen maturation	Sasaki et al. [87]
inhibition	ALKBHs (2OG-dependent AlkB homologue	Impaired DNA repair	Wang et al. [88], Chen et al. [89]
inhibition	FTO pathway (fat mass and obesity-associated protein)	RNA methylation, suppression of MYCL/CEBPA (CCAAT enhancer binding protein alpha)-associated pathways.	Su et al. [91]
inhibition	ATP synthase	Mitochondrial respiration, and mTOR signaling reduction	Fuet al. [92]
binding	DMNT1(DNA methyltransferase 1)	RIP3(receptor-interacting protein 3) downregulation	Yang et al. [93]
binding	BCAT (branched-chain amino acid transferase) transaminases	Impaired glutamate biosynthesis	McBrayeret. Al. [94]

5.5. IDH mutations in CNS tumors

Adults' most prevalent neurological cancers are gliomas [95]. The status of the IDH mutation is one of the most important tools of diagnosis of diffuseglioma; accordingly, they can be classified into IDH-wildtype and IDH-mutant type. IDHmutations are more common in low grade gliomas (LGGs) and secondary glioblastomas (GBMs) and are some of the first genetic alterations during the growth of these tumors[76]. IDH polymorphism often take place during glioma formation in its early stages and are insufficient alone for malignant transformation, they indeed, frequently develop subsequent additional genetic disorders such as tumor protein 53 (TP53) alterations, lack of ATP-dependent helicase ATRX, X-linked helicase II (ATRX), or co-deletion of chromosome region 1p/19q[96]. IDH mutations are among the most crucial criteria in glioma diagnostic evaluation. IDH alterations, for instance, are frequently found in defuse astrocytomas, next come TP53 and ATRX polymorphisms. As regard oligodendrogliomas, IDH abnormalities with 1p/19q co-deletion (with perhaps CIC and FUBP1 mutations) are prevalent. [97]. The presence of an IDH mutation can also help to distinguish between primary and secondary glioblastoms.[98]. Furthermore, because IDH mutations typically result in genome-wide DNA and histone hypermethylation, methylation screening can improve accuracy of classification of glioma even more. As a result, knowing whether the glioma patient has an IDH mutation or not can help physicians to classify the napalms and choose the best treatment options [96].

5.6. IDHs in other neurological disorders

5.6 .1 Neurodegenerative disorders

As a result of their critical role IDH enzymes in oxidation / reduction equilibrium and metabolic activity of the cell, they may be implicated in neurodegeneration[74]. NADPH provided byIDH1 and IDH2 in both cytoplasm and mitochondria, is required for the re-synthesis of glutathione which is neuroprotective against oxidative damage. Lipid peroxidation to proteins, and nucleic acids oxidation with subsequent structural, and functional abnormalities, were discovered to be enhanced asa as a consequence to diminished levels of glutathione reduced form in neural tissue autopsy taken from Alzheimer disease suffers after death[99]. Similarly, decreased levels of glutathione have been observed in AD and HD. So, glutathione impairment has an important a role in the pathogenesis of Parkinson’s disease (PD), AD, HD, ALS, and Friedreich’s ataxia [100].

5.6. 2 Degenerative disorders of the retina

IDH3A genetic disorders were described in people with hereditary disorders of the retina, that are distinguished by

gradual loss of photosensitive receptors and/or pigmented epithelium present in the retina and are a primary cause of permanent loss of vision in kids and adolescents. The most frequent inherited retinal disease is retinitis pigmentosa [74].

A diversity of IDH3 polymorphisms linked to RP had been discovered using whole-genome sequencing. Individuals having a homozygous missense mutation in IDH3A codon 304 had the most serious form, exhibiting juvenile encephalopathy along with peripheral and autonomic nervous systems affection, as well as retinitis pigmentosa[101].

6. Other biochemical markers in CNS trauma

6.1. Periostin

Periostin is a protein presents in the extracellular matrix with a molecular weight of 90-kD. It is a neurite outgrowth-promoting factor. It was foundto be increasingly expressed in rat brain tissues aftercerebral ischemia or subarachnoid hemorrhage. In patients with TBI, increased serum periostin concentrationsat admission were strongly relevant to the severity, and short-term mortality, which indicated that periostinin serum may be a useful prognostic biomarkerin patients with severe TBI [102].

6.2. Glial fibrillary acidic protein (GFAP)

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein presents in the cytoskeleton of astroglia. It has been indicated that GFAP may be used as a marker of traumatic brain injury (TBI) that is released in blood after central nervous system cell injury [103].

6.3. Myelin basic protein (MBP)

Myelin basic protein (MBP) is known as the second most abundant protein in myelin of the central nervous system. Since the 1980s, it has been considered as a biomarker of brain tissue damagedue to either trauma or disease [104].

Figure-1:summarizes biochemical markers released during CNS trauma.

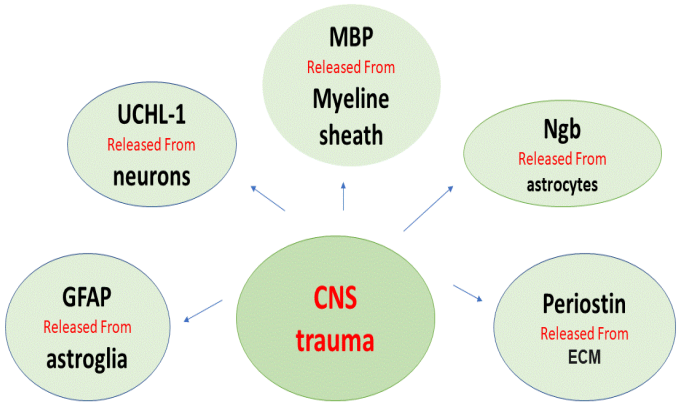

Figure 1. Biochemical markers released during neurological trauma.

Abbreviations: UCHL1: Ubiquitin C-terminal Hydrolase L1; MBP: Myelin basic protein; Ngb: neuroglobin; GFAP: Glial fibrillary acidic protein; ECM: extracellular matrix.

7. Other genetic markers in CNS tumors

7.1. RELA fusion

Chromothripsis, which includes chromosome 11q13.1, drives C11or f95-RELA fusions. In the nucleus, C11orf95-RELA fusion proteins play a role in activating the nuclear factor-B group regulatory proteins, which mediate cell response to inflammation and induce neural stem cells rapid transformation into malignancies such as ependymoma [105].

7.2. TERT (Telomerase reverse transcriptase) promoter mutations

C228T and C250T promoter mutations are the most common TERT mutations. In gliomas, TERT promoter mutations as well as prolonged telomere are predictors of decreased expected lifespan and radiotherapy ineffectiveness. This is commonly noticed in glioblastoma and oligodendroglioma[106].

7.3.O6-methylguanine-DNA methyltransferase methylation (MGMT)

The O6-methylguanine-DNA-methyltransferase (MGMT) gene codes for a DNA repair enzyme that can counteract the impacts of alkylating treatment agents like temozolomide. The introduction of methyl groups through alkylating chemotherapeutic agents causes DNA genotoxicity. So, a tumor with extensive MGMT expression is generally more resistant to chemotherapeutic drugs that target DNA at this site. This gene would be more expressed if its promoter area was not methylated, buthypermethylation of the MGMT promoter, will make the gene silenced. When the MGMT gene is active, the damage can be rapidly repaired. Methylation of the MGMT gene promoter has favorable prognostic and predictive value in glioblastoma patients, but it does not have a diagnostic valuein these patients [107].

Figure-2: summarizes genetic marrkers common in CNS tumors.

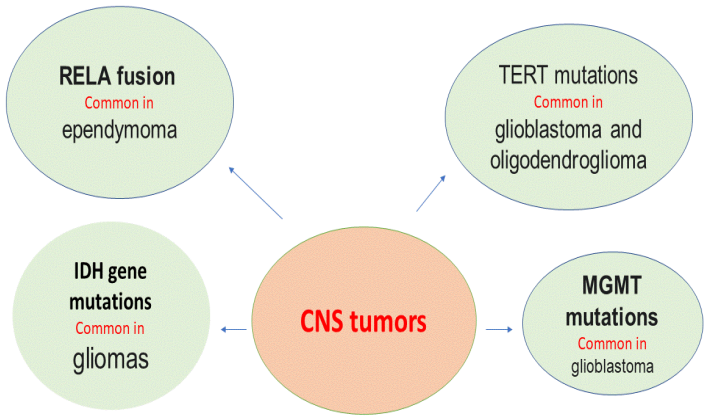

Figure 2. Common genes involved in neurological tumors.

Abbreviations: MGMT: O6-methylguanine-DNA methyltransferase methylation; IDH: isocitrate dehydrogenase; TERT: Telomerase reverse transcriptase.

CONCLUSION

Biochemical and genetic markers such as UCH-L1 and Ngb are promising tools

in diagnosis and classification of CNS trauma and tumors. Also, they can have a role in predicting the outcome of patients with TBI. IDH1 is a genetic marker of great importance in gliomas which are the most common type of CNS tumors. More research is needed on these markers to improve their role in clinical field.

REFERENCES

1. Montaser T, Hassan A. Epidemiology of moderate and severe traumatic brain injury in Cairo University Hospital in 2010. Critical Care. 2013 Apr;17(2): P320.

2. Kim, D. K., Lee, D. H., Lee, B. K., Cho, Y. S., Ryu, S. J., Jung, Y. H., Performance of Modified Early Warning Score (MEWS) for predicting in-hospital mortality in traumatic brain injury patients. Journal of clinical medicine.2021;10(9), 1915.

3.Siahaan, A. M. P., Japardi, I., Hakim, A. A. Serum concentration of ubiquitin c-terminal hydrolase-L1 in detecting severity of traumatic brain injury. In IOP Conference Series: Earth and Environmental Science.2018;125(1): p.012207. IOP Publishing.

4. Costanzo, M., Fiocchetti, M., Ascenzi, P., Marino, M., Caterino, M., Ruoppolo, M.Proteomic and bioinformatic investigation of altered pathways in neuroglobin-deficient breast cancer cells. Molecules.2021;26(8):2397.

5. Luyckx, E., Van Acker, Z. P., Ponsaerts, P., Dewilde, S. Neuroglobin expression models as a tool to study its function. Oxidative medicine and cellular longevity. 2019; 2019.

6. Schubart JR, Kinzie MB, Farace E. Caring for the brain tumor patient:family caregiver burden and unmet needs. Neuro Oncol 2008; 10: 61−72.

7. Yusoff AA, Zulfakhar FN, Sul'ain MD, Idris Z, Abdullah JM. Association of the IDH1 C. 395G> A (R132H) mutation with histological type in Malay brain tumors. Asian Pacific journal of cancer prevention: APJCP. 2016;17(12):5195.

8. Menon, D. K., Schwab, K., Wright, D. W., Maas, A. I. Position statement: definition of traumatic brain injury. Archives of physical medicine and rehabilitation.2010: 91(11): 1637-1640.

9. Saberi, B. Traumatic Brain Injury Classification Systems: GCS, Marshall, and Mayo Classifications. Glob J Anes & Pain Med. 2021; 4(4), 429 - 430.

10. Alalwan, Q., Dossary, H. A., Alsayegh, H., & Alothman, M. Cross-sectional imaging of head trauma: a retrospective analysis of the incidence, and imaging findings of traumatic brain injury in King Fahad Hospital, Al-Ahsa, Saudi Arabia. *IJMDC*. 2019; *3*(8): 663-8.

11. Langlois, J. A., Rutland-Brown, W., & Wald, M. M.The epidemiology and impact of traumatic brain injury:a brief overview. *The Journal of head trauma rehabilitation*. 2006; *21*(5): 375-378.

12. Åstrand, R., & Undén, J. Classification of head injury. In *Management of Severe Traumatic Brain Injury*.2020; (pp. 51-59). Springer, Cham.

13.Stein, S. C., & Spettell, C.The Head Injury Severity Scale (HISS): a practical classification of closed-head injury. *Brain injury*.1995, *9*(5): 437-444.

14. Ingebrigtsen, T., Romner, B., Kock-Jensen, C.Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries. *Journal of Trauma and Acute Care Surgery*. 2000; *48*(4): 760-766.

15. Wilson, L., Boase, K., Nelson, L. D., Temkin, N. R., Giacino, J. T., Markowitz, A. J., Manley, G. T.A manual for the

glasgow outcome scale-extendedinterview. *Journal of neurotrauma*. 2021; *38*(17): 2435-2446.
16. Ezzati, K., Yousefzadeh-Chabok, S., Rezaei, S., Reihanian, Z.Translation, Validity, and Reliability of Disability Rating Scale in Iranian Patients with Traumatic Brain Injury. *Archives of Trauma Research*. 2020;*9*(4):167.
17. Lee, Y. H., Chang, K. H., Escorpizo, R., Chi, W. C., Yen, C. F., Liao, H. F.,Liou, T. H. Accuracy of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) score as an objective assessment tool for predicting return-to-work status after head and neck cancer in male survivors. *Supportive Care in Cancer*. 2019;*27*(2):433-441.
18. Kang, Y., Ding, H., Zhou, H., Wei, Z., Liu, L., Pan, D., & Feng, S. Epidemiology of worldwide spinal cord injury: a literature review. *Journal of Neurorestoratology*. 2018;*6*(1): 3.
19.Van den Berg, M. E. L., Castellote, J. M., Mahillo-Fernandez, I.,de Pedro-Cuesta, J. Incidence of spinal cord injury worldwide: a systematicreview. *Neuroepidemiology*. 2010;*34*(3): 184-192.

20. Kirshblum, S. C., Burns, S. P., Biering-Sorensen, F., Donovan, W., Graves, D. E., Jha, A.,Waring, W.International standards for neurological classification of spinal cord injury (revised 2011). *The journal of spinal cord medicine. 2011*; *34*(6): 535-546.
21.McNeill, K. A.Epidemiology of brain tumors. *Neurologic clinics*.2016; *34*(4): 981-998.
22.Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H., ... & Satpathy, M.Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA oncology*. 2017; *3*(4): 524-548.
23. Patel, A. P., Fisher, J. L., Nichols, E., Abd-Allah, F., Abdela, J., Abdelalim, A., Fitzmaurice, C.Global, regional, and national burden of brain and other CNS cancer, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2019;*18*(4): 376-393.
24. Leece, R., Xu, J., Ostrom, Q. T., Chen, Y., Kruchko, C., & Barnholtz-Sloan, J. S. Global incidence of malignant brain and other central nervous system tumors by histology, 2003–2007. *Neuro-oncology*. 2017; *19*(11): 1553-1564.
25. Stupp, R., Hegi, M. E., Mason, W. P., Van Den Bent, M. J., Taphoorn, M. J., Janzer, R. C., National Cancer Institute of Canada Clinical Trials Group.Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *The lancet oncology*. 2009, *10*(5): 459-466.
26. Johnson, K. J., Cullen, J., Barnholtz-Sloan, J. S., Ostrom, Q. T., Langer, C. E., Turner, M. C.,Scheurer, M. E.Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. *Cancer Epidemiology and Prevention Biomarkers*. 2014; *23*(12): 2716-: 2736.
27. Gupta, A., & Dwivedi, T. A Simplified Overview of World Health Organization Classification Update of Central Nervous System Tumors 2016. *Journal of neurosciences in rural practice*. 2017; *8*(4): 629–641.

28. Bishop, P., Rocca, D., Henley, J. M. Ubiquitin C-terminal hydrolase L1 (UCH-L1): structure, distribution and roles in brain function and dysfunction. *Biochemical Journal*. 2016; *473*(16): 2453-2462.
29. Abdullah, A., Das, C., Flaherty, D. P. Ubiquitin C-Terminal Hydrolase L1: Biochemical and Cellular Characterization of a Covalent Cyanopyrrolidine-BasedInhibitor.Chembiochem: a European journal of chemical biology. 2020; 21(5): 712.
30. Wang, K. K., Kobeissy, F. H., Shakkour, Z.,Tyndall, J. A.Thorough overview of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein as tandem biomarkers recently cleared by US Food and Drug Administration for the evaluation of intracranial injuries among patients with traumatic brain injury. *Acute Medicine & Surgery*. 2021; *8*(1): e622.
31. Matuszczak, E., Tylicka, M., Komarowska, M. D., Debek, W., Hermanowicz, A.Ubiquitin carboxy-terminal hydrolase L1–physiology and pathology. Cell biochemistry and function. 2020; 38(5): 533-540.
32. Jackson P, Thompson RJ. The demonstration of new humanbrain-specific proteins by high-resolution two-dimensionalpolyacrylamide gel electrophoresis. J. Neurol. Sci. 1981; 49:429–38.
33. Wang, K. K., Yang, Z., Sarkis, G., Torres, I.,Raghavan, V. Ubiquitin C-terminal hydrolase-L1 (UCH-L1) as a therapeutic and diagnostic target in neurodegeneration, neurotrauma and neuro-injuries. *Expert opinion on therapeutic targets*. 2017; *21*(6): 627-638.
34. Hewitt, C. S., Krabill, A. D., Das, C., Flaherty, D. P.Development of ubiquitin variants with selectivity for ubiquitin C-terminal hydrolase deubiquitinases. *Biochemistry*. 2020; *59*(37): 3447-3462.
35. Nagamine, S., Kabuta, T., Furuta, A.,Yamamoto, K., Takahashi, A. and Wada, K.
Deficiency of ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) leads to vulnerability
to lipid peroxidation. Neurochem. Int. 2010; 57: 102–110.
35. Choi, J., Levey, A.I., Weintraub, S.T., Rees, H.D., Gearing, M., Chin, L.S. and Li, L.Oxidative modifications and down-regulation of ubiquitin carboxyl-terminalhydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases. J. Biol.Chem. 2007, 279, 13256–13264.
36. Gu Y, Lv F, Xue M. The deubiquitinating enzyme UCHL1 is afavorable prognostic marker in neuroblastoma as it promotes neuronal differentiation. J Exp Clin Cancer Res.2018; 37(1):258.
37. Tofaris, G. K., & Spillantini, M. G.Alpha-synuclein dysfunction in Lewy body diseases. *Movement disorders: official journal of the Movement Disorder Society*. 2005; *20*(S12): S37-S44.
38. Camara, M. L., Almeida, T. B., de Santi, F., Rodrigues, B. M., Cerri, P. S., Beltrame, F. L., Sasso-Cerri, E. Fluoxetine-induced androgenic failure impairs the seminiferous tubules integrity and increases ubiquitin carboxyl-terminal hydrolase L1 (UCHL1): Possible androgenic control of UCHL1 in germ cell death? *Biomedicine & Pharmacotherapy*. 2019; *109*: 1126-1139.
39. Matuszczak E, Tylicka M, Dębek W, Tokarzewicz A, Gorodkiewicz

E,Hermanowicz A. Concentration of UHCL1 in the serum of children
with acute appendicitis, before and after surgery, and its correlationwith CRP and prealbumin. J Invest Surg. 2018;31(2):136-141.
40. Gao, H., Freeling, J., Wu, P., Liang, A. P., Wang, X., Li, Y. UCHL1 regulates muscle fibers and mTORC1 activity in skeletal muscle. *Life sciences*. 2019; *233*: 116699.
41. Bilguvar, K., Tyagi, N. K., Ozkara, C., Tuysuz, B., Bakircioglu, M., Choi, M.,Gunel, M.Recessive loss of function of the neuronal ubiquitin hydrolase UCHL1 leads to early-onsetprogressive neurodegeneration. *Proceedings of the National Academy of Sciences. 2013, 110*(9): 3489-3494.
42. Goto, A., Wang, Y. L., Kabuta, T., Setsuie, R., Osaka, H., Sawa, A., Wada, K. Proteomic and histochemical analysis of proteins involved in the dying-back-type of axonal degeneration in the gracileaxonal dystrophy (gad) mouse. *Neurochemistry international*. 2009; *54*(5-6): 330-338.
43. Ciccone, L., Nencetti, S., Socci, S., Orlandini, E. Neuroglobin and neuroprotection: the role of natural and synthetic compounds in neuroglobin pharmacological induction. *Neural regeneration research*. 2021; *16*(12): 2353.
44.Burmester, T., & Hankeln, T.What is the function of neuroglobin? *Journal of Experimental Biology*. 2019; *212*(10): 1423-1428.
45. Costanzo, M., Fiocchetti, M., Ascenzi, P., Marino, M., Caterino, M., & Ruoppolo, M. (2021). Proteomic and bioinformatic investigation of altered pathways in neuroglobin-deficient breast cancer cells. *Molecules*, *26*(8), 2397.
46. Tosqui, P., & Colombo, M. F. Neuroglobin and cytoglobin: two new members of globin family. *Revista brasileira de hematologia e hemoterapia*. 2011; *33*: 307-311.
47. Fuchs, C., Burmester, T., & Hankeln, T. The amphibian globin gene repertoire as revealed by the Xenopus genome. *Cytogenetic and genome research*. 2006;*112*(3-4): 296-306.
48. Wen, H., Liu, L., Zhan, L., Liang, D., Li, L., Liu, D.,Xu, E.Neuroglobin mediates neuroprotection of hypoxic postconditioning against transient global cerebral ischemia in rats through preserving the activity of Na+/K+ ATPases. *Cell Death & Disease*. 2018; *9*(6): 1-18.
49. Ascenzi, P., di Masi, A., Leboffe, L., Fiocchetti, M., Nuzzo, M. T., Brunori, M., & Marino, M. Neuroglobin: From structure to function in health and disease. *Molecular aspects of medicine*. 2016; *52*: 1-48.
50. Keller 4th, T. S., Lechauve, C., Keller, A. S., Brooks, S., Weiss, M. J., Columbus, L.,Isakson, B. E.The role of globins in cardiovascularphysiology. *Physiological reviews*. 2022; *102*(2): 859-892.
51. Liu, J., Yu, Z., Guo, S., Lee, S. R., Xing, C., Zhang, C.,Wang, X. Effects of neuroglobin overexpression on mitochondrial function and oxidative stress following hypoxia/reoxygenation in cultured neurons. *Journal of neuroscience research*. 2009; *87*(1): 164-170.
52. Sun, Y., Jin, K., Mao, X. O., Zhu, Y., & Greenberg, D. A. Neuroglobin is up-regulated by and protects neurons from hypoxic-ischemic injury. *Proceedings of the National Academy of Sciences*. 2001; *98*(26): 15306-15311.
53. Baez, E., Echeverria, V., Cabezas, R., Ávila-Rodriguez, M., Garcia-Segura, L. M., Barreto, G. E. Protection by

neuroglobin expression in brain pathologies. *Frontiers in Neurology*. 2016; *7*: 146.
54. Li Y, Dai Y, Sun J, Xiang Y, Yang J, Dai S, Zhang X. Neuroglobin attenuatesbeta amyloid-induced apoptosis through inhibiting caspases activity byactivating PI3K/Akt signaling pathway. J Mol Neurosci. 2016; 58:28-38.
55. Brittain, T., Skommer, J., Raychaudhuri, S., & Birch, N. An antiapoptotic neuroprotective role for neuroglobin. *International journal of molecular sciences*. 2010;*11*(6): 2306-2321.
56. Baez, E., Echeverria, V., Cabezas, R., Ávila-Rodriguez, M., Garcia-Segura, L. M., Barreto, G. E. Protection by neuroglobin expression in brain pathologies. *Frontiers in Neurology*. 2016; *7*: 146.
57. Luyckx, E., Van Acker, Z. P., Ponsaerts, P., Dewilde, S. Neuroglobin expression models as a tool to study its function. *Oxidative medicine and cellular longevity*. 2019; *2019*.
58. Chen, H., Cao, H. L., Chen, S. W., Guo, Y., Gao, W. W., Tian, H. L.,Xue, L. X. Neuroglobin and Nogo-a as biomarkers for the severity and prognosis of traumatic brain injury. *Biomarkers*. 2015; *20*(6-7): 495-501.
59. Van Acker, Z. P., Declerck, K., Luyckx, E., Berghe, W. V.,Dewilde, S.Non-methylation-linked mechanism of REST-induced neuroglobin expression impacts mitochondrial phenotypes in a mouse model of amyotrophic lateral sclerosis. *Neuroscience*. 2019; *412*: 233-247.
60. Fiocchetti, M., Fernandez, V. S., Montalesi, E., Marino, M.Neuroglobin: A novel player in the oxidative stress response of cancer cells. *Oxidative medicine and cellular longevity*. 2019; *2019*.
61. Qin, H., Guo, Y., Zhang, C., Zhang, L., Li, M.,Guan, P.The expression of neuroglobin in astrocytoma. *Brain tumor pathology*. 2012; *29*(1): 10-16.
62. Pavlova, N. & Thompson, C. The emerging hallmarks of cancer metabolism.Cell Metab. 2016; 23:27–47.
63. Sun, P., Liu, Y., Ma, T., Ding, J. Structure and allosteric regulation of human NAD-dependent isocitrate dehydrogenase. *Cell discovery*. 2020; *6*(1): 1-15.
64.Jakob, C. G., Upadhyay, A. K., Donner, P. L., Nicholl, E., Addo, S. N., Qiu, W.,Hutti, J. E.
Novel modes of inhibition of wild-type isocitrate dehydrogenase 1 (IDH1): direct covalent modification of His315. *Journal of Medicinal Chemistry*. 2018, *61*(15): 6647-6657.
65. Zheng, J., Yates, S. P.,Jia, Z. Structural and mechanistic insights into the bifunctional enzymeisocitrate dehydrogenase kinase/phosphatase AceK. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2012; *367*(1602): 2656-2668.
66. OlsenJV, B., GnadF, M., KumarC, M., Mann, M.Global, in vivo, and site-specific phosphorylation dynamics in signaling networks. *Cell*. 2006; *127*(3): 635-648.
67. LaPorte, D. C., & Koshland, D. E. A protein with kinase and phosphatase activities involved in regulation of tricarboxylic acid cycle. *Nature*. 1982; *300*(5891): 458-460.
68. Zhang, X., Shen, Q., Lei, Z., Wang, Q., Zheng, J., & Jia, Z.Characterization of metal binding of bifunctional kinase/phosphatase AceK and implication in activity modulation. *Scientific reports*. 2019; *9*(1): 1-12.

69. Yang, B., Zhong, C., Peng, Y., Lai, Z., Ding, J.Molecular mechanisms of “off-on switch” of activities of human IDH1 by tumor-associated mutation R132H. *Cell research*. 2010; *20*(11): 1188-1200.
70Lin, A. P., & McAlister-Henn, L. Homologous binding sites in yeast isocitrate dehydrogenase for cofactor (NAD+) and allosteric activator (AMP). *Journal of Biological Chemistry*. 2003; *278*(15): 12864-12872.
71. Lin, A. P., Demeler, B., Minard, K. I., Anderson, S. L., Schirf, V., Galaleldeen, A., & McAlister-Henn, L. Construction and analyses of tetrameric forms of yeast NAD+-specific isocitrate dehydrogenase. *Biochemistry*.2011; *50*(2): 230-239.
72. Taylor, A. B., Hu, G., Hart, P. J., McAlister-Henn, L. Allosteric motions in structures of yeast NAD+-specific isocitrate dehydrogenase. *Journal of Biological Chemistry*. 2008; *283*(16): 10872-10880.
73. Bezerra, B. S., Belato, F. A., Mello, B., Brown, F., Coates, C. J., de Moraes Leme, J.osta-Paiva, E. M.Evolution of a key enzyme of aerobic metabolism reveals Proterozoic functional subunit duplication events and an ancient origin of animals. *Scientific Reports*. 2021; *11*(1): 1-11.
74. Tommasini-Ghelfi, S., Murnan, K., Kouri, F. M., Mahajan, A. S., May, J. L., & Stegh, A. H.Cancer-associated mutation and beyond: The emerging biology of isocitrate dehydrogenases in human disease. *Science Advances*. 2019; *5*(5): eaaw4543.
75. Sun, P., Ma, T., Zhang, T., Zhu, H., Zhang, J., Liu, Y., Ding, J.Molecular basis for the function of the αβ heterodimer of human NAD-dependent isocitrate dehydrogenase. *Journal of Biological Chemistry*. 2019; *294*(44): 16214-16227.
76. Kayabolen, A., Yilmaz, E.,Bagci-Onder, T. IDH Mutations in Glioma: Double-Edged Sword in Clinical Applications? *Biomedicines*. 2021; *9*(7): 799.
77. Lee, S. M., Koh, H. J., Park, D. C., Song, B. J., Huh, T. L., Park, J. W.Cytosolic NADP+-dependent isocitrate dehydrogenase status modulates oxidative damage to cells. *Free Radical Biology and Medicine*. 2002; *32*(11): 1185-1196.
78. Shechter, I., Dai, P., Huo, L., Guan, G. IDH1 gene transcription is sterol regulated and activated by SREBP-1a and SREBP-2 in human hepatoma HepG2 cells: evidence that IDH1 may regulate lipogenesis in hepatic cells. *Journal of lipid research*. 2003; *44*(11): 2169-2180.
79. Losman, J. A., & Kaelin, W. G.What a difference a hydroxyl makes: mutant IDH(R)-2-hydroxyglutarate, and cancer. *Genes & development*. 2013; *27*(8): 836-852.
80. Liu, S., Cadoux-Hudson, T., Schofield, C. J. Isocitrate dehydrogenase variants in cancer—Cellular consequences and therapeutic opportunities. *Current opinion in chemical biology*. 2020; *57*: 122-134.
81.Pirozzi, C. J., & Yan, H.The implications of IDH mutations for cancer development and therapy. *Nature Reviews Clinical Oncology*. 2021; *18*(10): 645-661.
82. Parsons, D. W., Jones, S., Zhang, X., Lin, J. C. H., Leary, R. J., Angenendt, P., Kinzler, K. W.An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008; *321*(5897): 1807-1812.
83. Yeung, B. H., Huang, J., An, S. S., Solway, J., Mitzner, W.,Tang, W. Y.Role

of isocitrate dehydrogenase 2 on DNA hydroxymethylation in human airway smooth muscle cells. *American journal of respiratory cell and molecular biology*. 2020; *63*(1): 36-45.
84. Turcan, S., Rohle, D., Goenka, A., Walsh, L. A., Fang, F., Yilmaz, E., Chan, T. A.IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature*. 2012; *483*(7390): 479-483.
85. Chowdhury, R., Yeoh, K. K., Tian, Y. M., Hillringhaus, L., Bagg, E. A., Rose, N. R.,Kawamura, A.The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. *EMBO reports*. 2011; *12*(5), 463-469.
86. Sulkowski, P. L., Oeck, S., Dow, J., Economos, N. G., Mirfakhraie, L., Liu, Y., Glazer, P. M. Oncometabolites suppress DNA repair by disrupting local chromatin signalling. *Nature*. 2020; *582*(7813): 586-591.
87. Sasaki, M., Knobbe, C. B., Itsumi, M., Elia, A. J., Harris, I. S., Chio, I. I. C., Mak, T. W. D-2-hydroxyglutarate produced by mutant IDH1 perturbs collagen maturation and basement membrane function. *Genes & development*. 2012; *26*(18): 2038-2049.
88. Wang, P., Wu, J., Ma, S., Zhang, L., Yao, J., Hoadley, K. A., Xiong, Y. Oncometabolite D-2-hydroxyglutarate inhibits ALKBH DNA repair enzymes and sensitizes IDH mutant cells to alkylating agents. *Cell reports*. 2015; *13*(11): 2353-2361.
89. Chen, F., Bian, K., Tang, Q., Fedeles, B. I., Singh, V., Humulock, Z. T.,Li, D. Oncometabolites d-and l-2-hydroxyglutarate inhibit the AlkB family DNA repair enzymes under physiological conditions. *Chemical research in toxicology*. 2017; *30*(4): 1102-1110.
90. Elkashef, S. M., Lin, A. P., Myers, J., Sill, H., Jiang, D., Dahia, P. L. Aguiar, R. C. IDH mutation, competitive inhibition of FTO, and RNA methylation. *Cancer cell*. 2017; *31*(5): 619-620.
91. Su, R., Dong, L., Li, C., Nachtergaele, S., Wunderlich, M., Qing, Y.Chen, J. R-2HG exhibits anti-tumor activity by targeting FTO/m6A/MYC/CEBPA signaling. *Cell*. 2018; *172*(1-2): 90-105.
92. Fu, X., Chin, R. M., Vergnes, L., Hwang, H., Deng, G., Xing, Y.,Huang, J. 2-Hydroxyglutarate inhibits ATP synthase and mTOR signaling. *Cell metabolism*. 2015; *22*(3): 508-515.
93. Yang, Z., Jiang, B., Wang, Y., Ni, H., Zhang, J., Xia, J.,Han, J. 2-HG inhibits necroptosis by stimulating DNMT1-dependent hypermethylation of the RIP3 promoter. *Cell reports*. 2017; *19*(9): 1846-1857.
94. McBrayer, S. K., Mayers, J. R., DiNatale, G. J., Shi, D. D., Khanal, J., Chakraborty, A. A., ... & Kaelin Jr, W. G. Transaminase inhibition by 2-hydroxyglutarate impairs glutamate biosynthesis and redox homeostasis in glioma. *Cell*. 2018; *175*(1): 101-116.
95. Ostrom, Q. T., Gittleman, H., Xu, J., Kromer, C., Wolinsky, Y., Kruchko, C., Barnholtz-Sloan, J. S. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro-oncology*. 2016; *18*(suppl_5), v1-v75.
96. Liu, Y., Lang, F., Chou, F. J., Zaghloul, K. A., Yang, C. Isocitrate dehydrogenase mutations in glioma: Genetics, biochemistry, and clinical indications. *Biomedicines*. 2020; *8*(9): 294.
97. Wen, P. Y., & Huse, J. T. 2016 World Health Organization classification

of central nervous system tumors. *CONTINUUM: Lifelong Learning in Neurology*. 2017; *23*(6), 1531-1547.
98. Chen, R., Smith-Cohn, M., Cohen, A. L.,Colman, H. Glioma subclassifications and their clinical significance. *Neurotherapeutics*. 2017; *14*(2): 284-297.
99. Dias, V., Junn, E., Mouradian, M. M. (2013). The role of oxidative stress in Parkinson's disease. *Journal of Parkinson's disease*. 2013; *3*(4): 461-491.
100. Johnson, W. M., Wilson-Delfosse, A. L., Mieyal, J.Dysregulation of glutathione homeostasis in neurodegenerative diseases. *Nutrients*. 2012; *4*(10): 1399-1440.
101. Fattal-Valevski, A., Eliyahu, H., Fraenkel, N. D., Elmaliach, G., Hausman-Kedem, M., Shaag, A., Elpeleg, O.Homozygous mutation, p. Pro304His, in IDH3A, encoding isocitrate dehydrogenase subunit is associated with severe encephalopathy in infancy. *Neurogenetics*. 2017; *18*(1): 57-61.
102. Dong, X. Q., Yu, W. H., Du, Q., Wang, H., Zhu, Q., Yang, D. B.,Jiang, L. Serum periostin concentrations and outcomes after severe traumatic brain injury. *Clinica Chimica Acta*. 2017; *471*: 298-303.
103. Lumpkins, K. M., Bochicchio, G. V., Keledjian, K., Simard, J. M., McCunn, M., Scalea, T. Glial fibrillary acidic protein is highly correlated with brain injury. *Journal of Trauma and Acute Care Surgery*. 2008; *65*(4): 778-784.
104. Wąsik, N., Sokół, B., Hołysz, M., Mańko, W., Juszkat, R., Jagodziński, P. P., Jankowski, R. Serum myelin basic protein as a marker of brain injuryin aneurysmal subarachnoid haemorrhage. *ActaNeurochirurgica*.2020; *162*(3): 545-552.
105. Ellison, D. W., Korshunov, A., & Witt, H. Ependymoma RELA fusion positive. *WHO Classification of Tumours of the Central Nervous System. 4th ed., Revised. Lyon: International Agency for Research Centre*. 2016; 112.
106. 10. Wiestler B, Capper D, Holland-Letz T, Korshunov A, von Deimling A, Pfister SM. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. *Acta Neuropathol.* 2013;126:443–51.
107. Håvik AB, Brandal P, Honne H, Dahlback HS, Scheie D, Hektoen M. MGMT promoter methylation in gliomas-assessment by pyrosequencing and quantitative methylation-specific PCR. *J Transl Med.* 2012;10:36.