Comprehensive Study and Age Determination of Biomarkers and Genetics of Traumatic Brain Injury

Abhishek Kumar Gautam[1*], Siddhant Yadav[2], Anjali Verma[3], Salil Singh[4]

[1]School of Studies in Forensic Science, Vikram University, Ujjain (M.P.)

[2]Department of Microbiology, Amity University, Lucknow (U.P.)

[3]Faculty, School of Studies in Forensic Science, Vikram University, Ujjain (M.P.)

[4]HOD, School of Studies in Forensic Science, Vikram University, Ujjain (M.P.)

Abstract:

TBI is a severe morbidity and death that is caused by a car accident or any kind of injury to the head. The capacity of microRNA (miRNA) molecules to control physiological and pathological processes has led to a rise in interest in miRNA profiling in this context. Potential assessment instruments for individuals with traumatic brain injury include biomarkers found in bodily fluids. These could function as internal markers of brain injury, providing important details on the changing molecular, cellular, and biochemical settings. The damaged brain may provide details through microRNAs (miRNAs). Everywhere in the body, these microscopic epigenetic chemicals are expressed. Determine clinical priorities for further research on this intriguing biomarker and the biology of miRNA in traumatic brain injury. The identification of novel biomarkers has been facilitated by advances in proteomics and more advanced laboratory procedures. Recovery from traumatic brain injury (TBI) is difficult due to ineffective treatments for neuronal damage, functional impairments, and cognitive abnormalities. NSE, S100, GFAP, calcium-binding protein, copeptin, IL-6, ferritin, lactate dehydrogenase (LDH), procalcitonin (PCT), glucose, and neutrophil gelatinase-associated lipocalin (N-Gal) are all proteins that are unique to neurons are a few examples of biomarkers/biomarkers. Radiographs and MRIs play an important role in the detection of TBI. In forensic science biomarkers, MRIs, and radiographs play an important role during post-mortem findings.

Keywords: Intracranial injury, non-coding RNA, molecular markers, MRI, Radiograph

1. Introduction:

Severe morbidity and demise as well as high direct and indirect expenses for both acute and long-term care are associated with intracranial injury, which is a significant worldwide issue for public health. Given the variability of TBI's clinical presentations and the variety of its individuals and traumas, accurate diagnosis and prognosis prediction can be difficult [1,2]. Knowing the biomarkers linked to traumatic brain injury and how to identify and interpret them might help with understanding the root cause of the condition and possible treatment approaches [3]. In order to find possible processes and targets for intervention, it is imperative that we comprehend the pathophysiology of traumatic brain damage while researching biomarkers and genetics in vitreous humor. Additionally, while examining biomarkers and genetics in vitreous humor, we must consider the edge and disadvantages of various methodologies. Over the past ten years, a variety of potential uses for the judicial traits applications involving RNA genotyping have become conceivable due to its capacity to control corporal and medical processes as well as proof of particular codes to an exact biological tissue. Because of their tiny size, which allows them to be retrieved even in severely damaged samples, microRNAs, or miRNAs, have recently attracted attention as potential forensic biomarkers in RNA profiling [4].

Clinically speaking, individuals with a persistent traumatic brain injury (TBI) may exhibit altered cognition and behavior, motor system impairments, and sensory system disruptions such as tactile, visual, olfactory, vestibular, and autonomic dysfunctions, pain, and sleep issues. Slow processing speed, decreased cognitive flexibility, emotional dysfunction, and poor executive function, attention, and memory are among the cognitive impairments that may even manifest in some individuals with modest injuries [5]. A genetic indication of a particular unhealthy or bodily state is called a biomarker.

Numerous techniques, including transcriptional, proteomic, and biochemical profiling, have been used in the search for molecular biomarkers since they can take many different forms. The process encompasses the identification of interesting compounds, creating, and validating biological assays, and retrospective longitudinal investigations on patients with known outcomes. [6]. Neuron-specific enolase (NSE), S100 calcium-binding protein (S100), glial fibrillary acidic protein (GFAP), Interleukin 6 (IL-6), lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), procalcitonin (PCT), glucose, Brain-derived neurotrophic factor (BDNF), neutrophil gelatinase-associated lipocalin (N-Gal), NF-κB, NRF2, PPAR-ϒ, and Pax 6 are a few biomarkers specific for brain damage [1, 11].

To achieve sufficient statistical ability to identify a connection, a gene variant with a low frequency, such as a single nucleotide polymorphism (SNP), would need to have an important influence size associated with it [7].

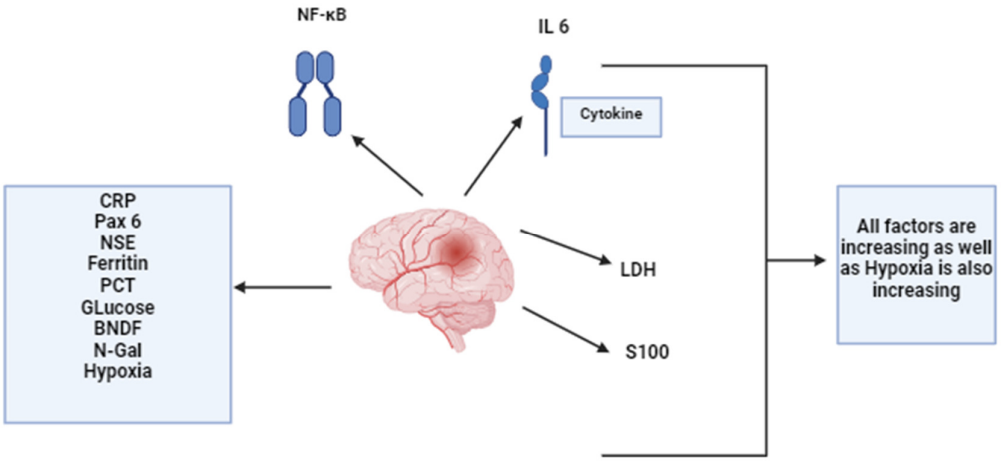


Fig 1: Diagrammatically illustration of biomarkers and hypoxia that are increasing which cause Traumatic Brain Injury (TBI). *Figure created with Biorender.com*

2. miRNA Mechanisms

Short (19–28 nucleotides), endogenous, and RNAs that are not encoded known as miRNAs function to control protein synthesis at the post-transcriptional phase. Primary microRNAs, or prim-miRNAs, are large precursor molecules (>1000 base pairs) that fold into a hairpin form when they are first produced in the nucleus. RNase Drosha cuts the pri-miRNA into stem-loop structures known as precursor microRNA (pre-miRNA), which range in length from 60 to 100 nucleotides. Pre-miRNA is exported into the cytoplasm, where miRNA: miRNA duplexes are created by the miRNA processing enzyme Decer. This duplex will split into two halves: the mature miRNA molecule will form from the other half, called the minor miRNA, and it will decay. By preventing protein translation or encouraging messenger RNA (mRNA) breakdown, the mature miRNA strand reduces the expression of particular gene targets when it is bound inside the microRNA-induced silencing complex (miRISC). Target genes are identified by the miRISC complex via "seed sequences" at the 5′ end of the miRNA that are complementary to the targeted mRNA target's 3′ region. Hundreds of distinct mRNAs can be recognized by the miRNA's seed sequence, and several miRNAs have the same seed sequence. Because the hairpin molecule sequences of miRNAs are similar, they are grouped into families. The greatest diversity and concentration of miRNAs are found in the central nervous system (CNS). The brain, spinal cord, or

peripheral nerves are thought to express 70% of all miRNAs. Following a brain injury, a series of biochemical events take place, including subacute healing, oxidative stress, apoptotic cell death, mechanical assault, and chronic remodeling. MiRNAs are excellent candidates for biomarkers because of their abundance, stability under varying pH conditions, resistance to enzyme destruction, and crucial function in transcriptional control. Less than an hour following a traumatic brain injury, brain-related miRNAs have been found in serum [8].

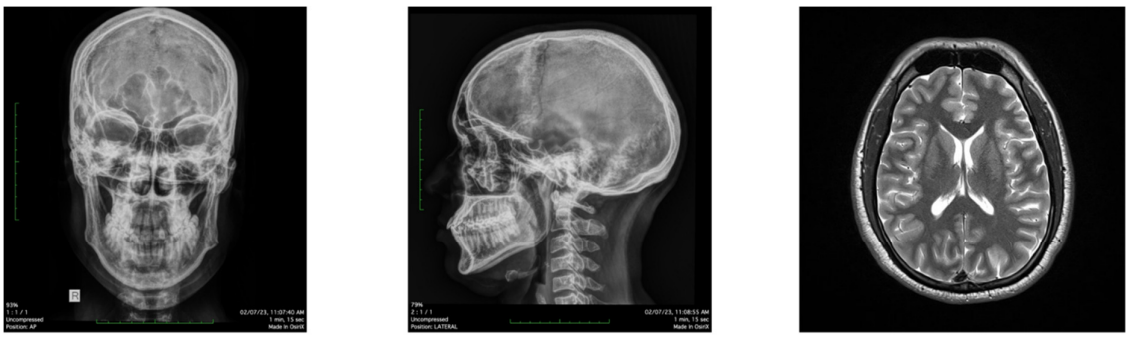
3. Techniques for finding TBI biomarkers

The two primary methodologies now used for biomarker discovery are "top-down" and "bottom-up" strategies, according to Noorbakhsh et al. There are intrinsic limits to both methods of organizing. To investigate the hundreds of biological materials that may be biomarkers, top-down approaches are ineffective. On top of that, these approaches strongly depend on the scant existing research and according to the researchers, limited capacity to construct close mental models of complex biological relationships [9].

4. Qualities of the perfect TBI biomarker:

The last 20 years have seen a significant surge in research on TBI biomarkers, with the majority of papers on the subject coming out in the previous ten years. We have learned that a clinically relevant biomarker has to have a number of important characteristics from our experience developing TBI biomarkers. These characteristics of a "perfect biomarker" would include such as, show a high degree of sensitivity and specificity for brain injury, classify patients according to the severity of their injuries, emerge quickly in a biological fluid that is easily accessible, offer details on the mechanisms underlying the injury, possess precisely defined biokinetic properties, track the progression of the illness and its response to treatment, forecast functional outcome, and be easily measured using widely accessible, basic techniques [10].

5. Result and Discussion:



(A) (B) (C)

Fig 2: (A) X-ray of the skull of the Human brain (Lateral), (B) X-ray of the skull of the Human brain (AP), (C) MRI imaging of the brain.

X-ray of Fig 2: (A) and (B), and MRI of Fig 2: (C), results and age assessment criteria for a young adult male(age>18.0 years). The Indian-born guy who was being examined stated that he was 26 years old.

In X-rays of Fig 2: (A) and (B), we found that shattered skull bone involving the parental bone posterior to the coronal suture, and in Magnetic Resonance Imaging (MRI) of Fig 2: (C), we found that due to the shattered skull bone and the head injury, and the others history of injuries of that patient cause the Traumatic Brain Injury (TBI).

In Forensic Science person's age and disease play an important role during post-mortem. Biomarkers also play an important role in any kind of disease-causing body or any post-mortem of cadavers. Both MRI and X-rays play an important role in age estimation also. One of the primary causes of mortality and disability is traumatic brain injury (TBI), which can result in neurological damage and mental problems (posttraumatic stress disorders). Assessing the role of trauma and medical malpractice in deaths, such as missed diagnoses and incorrect treatment, is crucial for determining the likelihood of survival [1].

6. Conclusion:

X-rays and MRIs play an important role in age estimation as well as the finding of traumatic brain injury (TBI).

Several biomarkers help find the specific brain damage. Biomarkers are used as a prognostic tool for the finding of the TBI. In the clinical setting, miRNA profiling has drawn more attention as a means of elucidating the pathophysiological processes underlying a number of disorders and offering recommendations for novel treatment approaches. Since miRNA profiling approaches yield valuable information, especially when combined with regular forensic investigations conducted in a multidisciplinary manner, translating them to the forensic context has also assumed paramount relevance [4].

7. Conflict of interest:

According to the author, this manuscript is free of any conflict of interest.

8. Funding:

This study has not received any funding.

9. Authors Contribution:

Author- 1, and 2 collected the raw data for this paper and the X-rays and MRI. Author- 3, and 4 guided us in writing this review paper.

10. Acknowledgement:

We acknowledge all authors to contribute the collected data from the related review paper. We also acknowledge the encouragement received from Centre of Bio-Medical Research (CBMR), Lucknow (U.P.) and Vidya Health Imaging, Gwalior (M.P.).

11. Abbreviations:

TBI: Traumatic Brain Injury

MRI: Magnetic Resonance Imaging

miRNA: MicroRNA

NSE: Neuron-specific enolase

S100: Calcium-binding protein

GFAP: Glial fibrillary acidic protein

LDH: Lactate dehydrogenase

BDNF: Brain-derived neurotrophic factor

IL-6: Interleukin 6

CRP: C-reactive protein

N-Gal: Neutrophil gelatinase-associated lipocalin

PCT: procalcitonin

SNP: Single nucleotide polymorphism

mi(RISC): microRNA-induced silencing complex

CNS: Central Nervous System

NF-κB: Nuclear factor kappa light chain enhancer of activated B cells

NRF2: Nuclear factor erythroid 2

PPAR ϒ: Peroxisome proliferated- -activated receptor

Pax 6: Paired box protein

12. Reference:

[1] Lanzilao, L., Bianchi, I., Grassi, S., Defraia, B., Brogi, M., Da Ros, M., Biagioli, T., Fanelli, A., Pinchi, V., & Focardi, M. (2023). Biomarkers of traumatic brain injury in vitreous humor: A pilot study. *Forensic Science International*, *350*, 111782. https://doi.org/10.1016/j.forsciint.2023.111782

[2] Ahuja, C. S., Mothe, A., Khazaei, M., Badhiwala, J. H., Gilbert, E. A., Kooy, D., Morshead, C. M., Tator, C., & Fehlings, M. G. (2020). The leading edge: Emerging neuroprotective and neuroregenerative cell-based therapies for spinal cord injury. *Stem Cells Translational Medicine*, *9*(12), 1509–1530. https://doi.org/10.1002/sctm.19-0135

[3] Futran, N. D., Farwell, D. G., Smith, R. B., Johnson, P. E., & Funk, G. F. (2005). Definitive management of severe facial trauma utilizing free tissue transfer. *Otolaryngology–Head and Neck Surgery*, *132*(1), 75–85. https://doi.org/10.1016/j.otohns.2004.08.013

[4] Albano, G. D., Stassi, C., Argo, A., & Zerbo, S. (2023). An overview on the use of mirnas as possible forensic biomarkers for the diagnosis of traumatic brain injury. *International Journal of Molecular Sciences*, *24*(7), 6503. https://doi.org/10.3390/ijms24076503

[5] Slavoaca, D., Muresanu, D., Birle, C., Rosu, O. V., Chirila, I., Dobra, I., Jemna, N., Strilciuc, S., & Vos, P. (2020). Biomarkers in traumatic brain injury: New concepts. *Neurological Sciences*, *41*(8), 2033–2044. https://doi.org/10.1007/s10072-019-04238-y

[6] Hergenroeder, G. W., Redell, J. B., Moore, A. N., & Dash, P. K. (2008). Biomarkers in the clinical diagnosis and management of traumatic brain injury. *Molecular diagnosis & therapy*, *12*, 345-358.

[7] Lipsky, R. H., & Lin, M. (2015). Genetic predictors of outcome following traumatic brain injury. *Handbook of clinical neurology*, *127*, 23-41.

[8] Atif, H., & Hicks, S. D. (2019). A review of microrna biomarkers in traumatic brain injury. *Journal of Experimental Neuroscience*, *13*, 117906951983228. https://doi.org/10.1177/1179069519832286

[9] Feala, J. D., AbdulHameed, M. D. M., Yu, C., Dutta, B., Yu, X., Schmid, K., Dave, J., Tortella, F., & Reifman, J. (2013). Systems biology approaches for discovering biomarkers for traumatic brain injury. *Journal of Neurotrauma*, *30*(13), 1101–1116. https://doi.org/10.1089/neu.2012.2631

[10] Papa, L., Robinson, G., Oli, M., Pineda, J., Demery, J., Brophy, G., ... & Hayes, R. L. (2008). Use of biomarkers for diagnosis and management of traumatic brain injury patients. *Expert opinion on medical diagnostics*, *2*(8), 937-945.

[11] Rai, V., Mendoza-Mari, Y., M. Radwan, M., Brazdzionis, J., A. Connett, D., E. Miulli, D., & K. Agrawal, D. (2024). Transcriptional and translational regulation of differentially expressed genes in yucatan miniswine brain tissues following traumatic brain injury. *Journal of Bioinformatics and Systems Biology*, *07*(01). https://doi.org/10.26502/jbsb.5107080