Original Article: Functional Investigation of Useful Biomarkers in the Diagnosis of Superficial Head Injury

Mohsen Nabiuni[1®], Jaber Hatam[2], Maryam Milanifard[3], Elham Seidkhani[4], Amin Jahanbakhshi[5*]

1. Assistant Professor of Neurosurgery, Spine Fellowship, Faculty Member, chief of Neurological surgery Department, Iran University of Medical Sciences, Tehran, Iran. Email: nabiuni_m@yahoo.com
2. Department of Neurosurgery, Faculty of medicine, Iran university of medical sciences, Tehran, Iran. Email: jaber.hatam@yahoo.com
3. Researcher, Department of Anatomical Sciences, School of Medicine, Iran university of Medical Sciences, Tehran, Iran. Email: maryammilani837@yahoo.com
4. Department of Anatomical Sciences, School of Medicine, Iran university of Medical Sciences, Tehran, Iran. Email: e.seidkhani@gmail.com
5. Associate Professor of Neurosurgery, Skull Base Research center, Iran university of Medical Sciences, Tehran, Iran. Email: amin.jahan@gmail.com

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Citation M. Nabiuni, J. Hatam, M. Milanifard, E. Seidkhani, A. Jahanbakhshi, **Investigation of Types of Neuropathies in the Brain and Nerves,** *EJCMPR* . 2022; 1(5):99-110.

https://doi.org/10.5281/zenodo.8047104

Article info:
Received: **01 May 2022**
Accepted: **16 December 2022**
Available Online:
ID: **EJCMPR-2205-1060**
Checked for Plagiarism: **Yes**
Peer Reviewers Approved by:
Dr. Amir Samimi
Editor who Approved Publication:
Dr. Frank Rebout

Keywords:
football, head injury, athlete, chronic traumatic, biomarker.

ABSTRACT

In American football, athletes regularly suffer minor head injuries. In fact, these blows are those that are not strong enough to cause symptoms of brain damage or even clinical symptoms. However, the repetition of these blows during a football season is associated with changes in neurophysiology and neuropsychology in athletes, and their accumulation in the long term can be the cause of severe neurological diseases such as Alzheimer's and chronic traumatic encephalopathy (CTE). Because minor head concussions do not cause symptoms, it is very difficult to ascertain brain damage and determine when an athlete should be out of action. To conduct these experiments, Oliver and his colleagues used a simple and readily available diagnostic test to identify and monitor minor head impacts in sample athletes during a football season. They also emphasized that it is better to periodically measure the biomarkers of head injuries. A new study from the University of Eastern Finland shows that certain plasma microRNAs can serve as diagnostic biomarkers in mild concussion injury. Biomarkers have been discovered in an animal model and successfully used to diagnose mild brain injury in a subgroup of patients. This study was published in the International Journal of Molecular Sciences.

Corresponding Author: Mohsen Nabiuni (nabiuni_m@yahoo.com)*

Introduction

Mild brain injury is difficult to detect with conventional contemporary imaging methods. In fact, most patients do not show visible structural brain damage that can be detected by computed tomography, even without structural damage, the diagnosis of mild brain damage is very important [1-3]. Because the ability to work in patients and their quality of life is deteriorating. There is a major unmet medical need to identify accurate, cost-effective, and widely available diagnostic biomarkers that can be used to better diagnose patients with mild traumatic brain injury and guide them toward timely symptomatic treatment and rehabilitation. Blood-based biomarkers enable cost-effective and minimally invasive diagnosis. Previous studies have shown that many biomarkers hold promise for describing the severity of brain damage and that they can provide information at the molecular level about ongoing pathological changes. In the newly published study, the researchers sought to find microRNAs that could serve as biomarkers for the diagnosis of traumatic brain injury. MicroRNAs or miRNAs are small RNA molecules that regulate the expression of protein-coding genes. Researchers sequenced blood plasma samples from an animal model after mild and severe brain damage. miRNAs showing the highest potential based on sequencing data were selected for further analysis based on polymerase chain reaction (PCR) [4-6]. Dr. Nora Puhaka from the AI Virtanen Institute for Molecular Sciences at the university said: "We are developing a suitable analysis and measurement method especially for miRNAs, which are found in small amounts in plasma, and this method is based on digital droplet PCR. Is. Humans and animals share many similar miRNAs, making them excellent candidates for studies where results obtained in animal models are applied to humans [7-9]. However, reproducing the results of different studies and different data sets is challenging. For this reason, evaluating the quality of measurement methods and reproducibility is a very important part of biomarker research [10-12]. The aim of the newly published study is to identify plasma miRNA biomarkers that are sensitive and specific to mild brain injury in an animal model and to investigate whether they can also be used to detect traumatic brain injury in humans. We found two interesting biomarkers in the animal model, plasma miRNAs miR-9a-3p and miR-136-3p, which we then decided to analyze in blood samples taken from brain-damaged patients. Plasma miR-9a-3p and miR-136-3p proved to be potential biomarker candidates for the diagnosis of mild brain injury in both animal models and patients.

Both of these miRNAs are more abundant in the brain than in other tissues, and their increased levels in plasma are likely due to brain injury and its severity. However, further research in larger patient groups is still needed. The study was conducted by the research group of Prof. Asla Pitlane in collaboration with Kuopio University Hospital [13-15]. Traditional laboratory analysis has been largely complemented by modern bioinformatics and machine learning methods. In this study, Oliver and colleagues defined a blood sampling schedule to fit the schedule of an academic football program.

To test the feasibility of this method, they investigated the usefulness of two common biomarkers in head injury and severe traumatic brain injury, namely Tau protein and Neurofilament light polypeptide NF-L. The researchers collected blood samples from 35 NCAA football players on seven different days, starting before the start of training camp and continuing until three weeks after the end of the season [16-18]. The researchers wanted to investigate the fluctuations of Tau plasma concentration and NF-L serum concentration in athletes during a football season to find out in which one, the number and number of head hits are different.

Those athletes who showed signs of concussion were excluded from further tests. The time of blood sampling was adjusted to the convenience of players and coaches, which was usually between 36 and 72 hours after a game or training session during the competition period. 20 football players were selected as members of the main team and 15 as reserve players. Since it is likely that the people in the main team will be

exposed to head blows in repeated games more than the reserve players. Therefore, the researchers expected that the concentration of biomarkers of brain trauma would increase in them compared to the reserve subjects who were considered as the control group in this study, but the analysis of blood samples showed that the concentration of Tau during the competition season compared to the values It decreased before the start of the season in both groups of players, but by examining the marker, the researchers in this study concluded that the amount of NF-L in the blood serum can be a reliable marker for brain damage. These findings can make doctors have a useful tool in diagnosing brain injuries following soft and frequent blows to the head of soccer players [19].

Concussions are more common than sports injuries

As people return to regular activities after the quarantine and restrictions of covid-19, when concussion rates have decreased, concussions are becoming more common again. About 1% of Canadians suffer a concussion each year, with an estimated 400,000 concussions in Canada alone. Worldwide, this number reaches more than 40 million people annually [20-22]. Concussion is a critical public health concern. Up to 30% of children and adults develop permanent problems after a concussion that reduces their quality of life and prevents them from returning to work, sports, school, and other activities [23].

Prevention, diagnosis and treatment

Important questions remain regarding the prevention, diagnosis, and treatment of concussion. In 2019, the parliamentary subcommittee on sports-related concussion in Canada called for the creation of a national expert group and a coordinated national research program [24-26]. In response, the Canadian concussion network was launched in 2020 to develop a Canadian research program that encompasses all causes of concussion, as well as to support knowledge translation to bring research evidence into clinical practice where it can improve patient care. It was launched. We are all members of the Canadian concussion network's executive committee or advisory council [27-29]. Our team includes a neuropsychologist, neurosurgeon and neurologist. We are all active researchers whose interests reflect the broader concussion research community in Canada, and two of us are clinicians [30-32]. Some recent developments in brain research in Canada, including those affected by concussions, may come as a surprise to readers.

Who gets a concussion?

Concussions don't just happen in sports or only in teenagers and young adults, but it affects people of all ages and backgrounds. Young children and the elderly often suffer concussions when they fall. Intimate partner violence has recently been recognized as a common cause of traumatic brain injury, with traumatic brain injury occurring in 80% of survivors, mostly women. Concussion and traumatic brain injury are also very common among people experiencing homelessness. About 35 percent of study subjects who experienced homelessness reported a head injury with symptoms of traumatic brain injury [33-35]. More research is needed on concussion among systemically disadvantaged groups, particularly Indigenous people who experience greater rates of injury. Building on Canada's many advances in sports-related concussion research, we must now ask how we can best prevent, diagnose and treat all concussions.

Prevention of sports-related concussions

The best concussion is the one that never happens. Prevention of sports-related concussions is a major focus of brain research in Canada. When body checking was shown to increase the risk of concussions in youth hockey, policy changes that did not allow body checking for players under 13 resulted in a reduction of more than 4,500 concussions per year. One of the largest studies of mouthguards to date has recently found that they likely prevent concussions in youth ice hockey. This evidence is of concern to parents concerned

about their children's participation in contact sports and may encourage sports organizations to implement policies requiring mouth guards. More broadly, parachute is Canada's largest charity dedicated to injury prevention and leads the concussion Coordination project supported by the public health agency of Canada in partnership with sport Canada. The goal of this project is to develop consistent concussion guidelines and protocols across more than 50 sports in Canada based on the Canadian guidelines on concussion in sport, which are based on scientific evidence [36].

Concussion diagnosis with biomarkers

Concussions are usually not visible using standard diagnostic neuroimaging tools such as CT scans. Diagnosing a concussion depends mainly on observing symptoms such as unconsciousness or vomiting and reporting symptoms such as headache, dizziness, or brain fog. However, injuries are not always directly visible and people cannot or do not always report their symptoms accurately [37-39]. Canadian researchers are investigating biomarkers of concussion, using biological fluids such as saliva or blood or advanced neuroimaging that may eventually be used at the side or in the emergency room to more accurately identify concussions. In collaboration with Statistics Canada, age-based reference intervals are being developed for blood-based biomarkers that can be used in concussion diagnosis across the lifespan [40].

Predicting concussion outcomes

When a child suffers a concussion, parents want to know their prognosis and how long it will take to recover. Although most children recover within two to four weeks, some have longer symptoms [41-43]. Researchers have developed a clinical prediction rule for children and adolescents that can be used to inform families about the likelihood of persistent symptoms. Clinicians can reassure parents of children at low risk and provide help for those at higher risk based on readily available information [44].

Promote recovery from concussion

People with concussions were told to rest in a dark room until their symptoms stopped. However, we now know that resting for more than a day or two can slow recovery. Instead, early resumption of activity and even low-intensity exercise can improve recovery and reduce persistent symptoms [45-47]. Researchers are also developing effective, targeted treatments for persistent symptoms. For example, cognitive behavioral therapy for insomnia is very effective in reducing the sleep problems that often occur after a concussion.

The relationship between headache and brain diseases

The Football Association of England has welcomed the results of recent research which shows that repeated blows to the head can cause degenerative brain diseases. Research conducted by Harvard university, Oxford university, Brooks university, and 12 other academic institutions provides evidence that chronic traumatic encephalopathy (CTE) can be linked to hemispheric blows such as head blows. Analysts of recent research have called for immediate protection measures in contact sports and say [48-50]: There are clear signs that force us to focus on the immediate implementation of programs to reduce this disease, especially for children. This type of dementia can lead to dramatic changes in mood, behavior, and cognition, and it will be incurable. Currently, CTE can only be diagnosed through a post-mortem examination, but efforts are underway to develop in-vivo biomarkers where the disease can also be detected ante-mortem. The FA has helped advance research in this area. After the field study, our research group also came to the same conclusion that soccer should look for ways to minimize and eliminate repetitive head impacts [51-53]. This has led to recent changes to header protocols in English football. Where we have introduced the most comprehensive guidelines and strictest restrictions of anywhere in the world, covering youth and adult play at all levels. We need more awareness for parents, athletes and policy makers and next season we will see new training programs by the professional leagues to all

players and we will continue to work to further raise awareness [54].

We also welcome the study recommendation to better understand the mechanism of CTE and the development of biomarkers to detect CTE in vivo. We have discussed this with our research group in the past and they have recommended that we focus on specific research in football. The FA will trial the elimination of headers in all under-12 age groups. By the start of the 2021-2022 season, the league had also introduced guidelines limiting professional players to 10 high-powered headers. New concussion rules were introduced to the Premier League in February 2021, allowing a player with a suspected brain injury to be replaced without forfeiting the number of substitutions. Head trauma is the most common and mildest type of brain trauma, and research by these researchers has shown that head trauma causes the release of a protein called glial filamentous acidic protein (GFAP).

This protein can cross the blood-brain barrier and enter the general blood circulation in the body. So, it's measurable and can be tracked up to a week after a head injury. Dr. Linda Papa, an emergency medicine specialist and one of the authors of this research, says: The symptoms of a head injury, or in other words, a mild or moderate concussion, may be very mild and often appear late, in many cases even a few days later. This method can provide doctors with an important tool for simple and accurate diagnosis, especially in children, so that they can perform the appropriate treatment with confidence. If the problem of these people is not diagnosed correctly and proper treatment is not done, it may cause long-term complications. According to the researchers, the measurement of this protein can lead to rapid surgery for those who are at risk of death or severe permanent complications due to brain damage [55].

Dr. Papa says: Doctors really want to reduce the number of CT scans in patients, especially children. Because they are more sensitive to radiation effects. Fortunately, this simple blood test gives us almost as much information as a CT scan. Dr. Papa says: Using this method will revolutionize the way of examining and diagnosing head trauma. He says: "We have diagnostic blood tests for various body organs such as heart, kidney and liver, but until now we have no reliable blood test to evaluate brain damage due to trauma." We think this blood test will change this situation.

Brain damage is linked to changes in gut bacteria

In order to find a connection between the changes in different organs of the body after a brain injury, scientists went to the gut bacteria and by conducting tests on 33 football players, they found that the concussion has changed the gut microbiome [56-58]. In order to find the connection between the changes in different organs of the body after a brain injury, scientists went to the intestinal bacteria and by conducting tests on 33 football players, they found that the concussion changed the intestinal microbiome and led to the production of certain proteins in the body, which through the test Blood and urine are traceable [59]. These changes help doctors to determine the extent of the patient's recovery. When there is a blow to the head, such as a skull fracture, the changes can be seen through X-ray imaging or a CT scan. On the other hand, microscopic changes occur in the body that damage nerve cells. These changes are so subtle that it is very difficult to detect them. Sometimes the patient has symptoms such as dizziness, blurred vision or nausea, which help doctors in diagnosis and treatment [60]. In some cases, the condition of the patient is such that it is difficult to diagnose the condition. Researchers believe that brain damage may activate certain biomarkers in the body that can be used for timely and definitive diagnosis. In recent years, the US food and drug administration has confirmed this idea by showing that a specific protein, KRAS G12C, is produced in the body after brain damage and can be detected through a blood test. Saliva and urine tests are other methods to check the presence of the mentioned protein. Recently, scientists have found that gut bacteria are linked to brain damage [61].

By studying animal models and cell cultures, they found promising signs describing this relationship. The research team tested blood,

stool and urine samples from 33 college football players over the course of a season. The said samples were collected at three-time intervals during the season to be useful for examining changes in the intestinal microbiome. The researchers found that the level of two types of intestinal bacteria decreases significantly with brain injury.

They also found a connection between the said protein and intestinal bacteria. Explaining this finding, the scientists said: probably the inflammation caused by brain damage causes the proteins and molecules circulating in the body to change, break the intestinal barrier and change the intestinal bacteria and its metabolism. Further research showed that the KRAS G12C protein regenerates itself up to 48 hours later. The researchers wrote in their paper: Detecting changes in the gut microbiome will help improve concussion diagnosis after head injury. Different biomarkers of the body that change due to concussion are used to measure the patient's recovery rate. Scientists believe that the patient is not cured until the gut microbiome returns to normal.

The risk of Alzheimer's disease in patients with corona virus

Covid infection and Alzheimer's disease have similar biomarkers of brain damage. Blood samples show that the accumulation of these biomarkers of brain damage occurs faster and at higher levels in covid. After almost two years of the corona virus epidemic, researchers are still looking for what happens in the brains of the survivors of this infection. We know that the virus can cause a wide range of neuropsychological symptoms in some infected people, from brain fog and sensory problems to strokes and long-term delusions.

In long-term covid patients, these symptoms remain for months, and of course, the experience of past epidemics has also shown that these brain injuries can be lifelong. The link between covid infection and the onset of dementia is not yet clear, and researchers need years of research to fully understand such a relationship, but recent evidence has shown that these diseases share similar biomarkers of brain damage. According to a new study, a short-term Covid infection appears to cause higher levels of blood proteins associated with neurodegeneration than Alzheimer's disease. NYU Grossman School of Medicine researchers analyzed two months of data from the beginning of the coronavirus pandemic from March to May 2020, the results of which were recently published in the Journal of the Alzheimer's Association. In this data, researchers found higher levels of seven different biomarkers of neurodegeneration in Covid patients with neurological symptoms.

The level of these biomarkers was much higher in patients who died in the hospital than in recovered patients, indicating a relationship between the severity of the disease and the severity of brain damage. In addition, these data showed that some of the markers of brain damage in hospitalized patients with covid are significantly higher than in patients with Alzheimer's disease.

In one case, the biomarker level in people with covid was more than double that of people with Alzheimer's. The findings of this study show that patients hospitalized for covid infection, especially those who experience neurological symptoms during their acute infection, may show a level of brain damage markers that is at the level of Alzheimer's disease or even higher. In this study, 251 patients with an average age of 71 years who were cognitively healthy and hospitalized due to corona virus were identified. The researchers examined patients who had neurological symptoms associated with covid and, if possible, compared the levels of neurodegeneration biomarkers in these patients with 161 Alzheimer's patients who did not have covid. Using a new precision diagnostic technology, the team then measured the extent of brain damage in all participants to detect seven different biomarkers for neurodegeneration, all associated with the death or dysfunction of neurons, in their blood plasma and serum. These biomarkers include two beta-amyloid proteins and two tau proteins, which also accumulate in the brains of people with Alzheimer's and other dementias.

Using a precision diagnostic technology, the research team then measured the extent of brain

damage in all participants by determining seven different blood biomarkers for neurodegeneration, all of which are associated with the death or dysfunction of neurons. These biomarkers included two beta amyloid proteins and two tau proteins.

The most striking difference between the two groups was in the levels of neurofilament light chain, a neuronal protein associated with a number of neurological diseases, including Alzheimer's. Previous research has shown that these neurofilaments may accumulate three to four times faster in people with Alzheimer's disease than in people with cognitive health. Now, a new study shows that in patients with covid, the level of these neurofilaments was almost twice as high as in people with Alzheimer's, a difference of 179%. What the researchers found was that the participants who were hospitalized due to a covid infection had, on average, 60% more biomarkers associated with neurodegeneration in their blood than those with Alzheimer's.

In people who died due to covid, they had more than twice these brain damage biomarkers compared to the survivors, but the question is whether the increased level of brain damage biomarkers in these patients means that they will suffer in the future. Alzheimer's or other types of dementia? Current data is not enough to answer this question accurately.

Studies conducted on traumatic brain injury show that brain damage biomarkers increase in these patients, but the follow-up of these patients showed that they do not necessarily develop Alzheimer's disease or related dementias in the future, but the risk dementia increases in them. Findings like this raise the concern that maybe the covid infection leads to permanent cognitive disorders and even Alzheimer's symptoms.

The corona virus has infected hundreds of millions of people around the world, and the prospect of ending the pandemic is still unclear, so it is necessary to continue to study what this virus does to our body and brain. This study was conducted at the very beginning of the epidemic, and since Alzheimer's disease can take years from the time the first biomarkers appear to the onset of symptoms. There is currently no way of knowing what the link between Covid and Alzheimer's will ultimately be. In fact, long-term studies are needed to determine whether patients infected with covid-19 are at an increased risk of developing Alzheimer's disease in the future, or whether they improve over time and this risk is eliminated.

Conclusion

According to the results of a new research by a group of researchers from Norway and Slovakia, hitting the ball with the head in soccer leads to minor damage to brain cells and possible long-term complications. To what extent does head impact in football endanger the athlete's health? This question has been discussed in sports and medical circles for years. Now, the result of new scientific research indicates that a slight brain damage occurs after hitting the head with the ball. A group of researchers from Norway and Slovakia have published the details of their scientific investigation in this field. In the framework of this scientific research, the researchers examined the blood samples of 89 professional football players.

These blood tests were taken in three different conditions. In the first case, a player's blood sample is tested after colliding with another player and falling to the ground. In the next case, the football player's blood sample is analyzed after the special practice of hitting the ball with the head, and in the third case, the blood of the player who did not hit the ball with his head at all during training is tested.

In the blood samples taken from the athletes after the special practice of hitting the ball with the head and after the players collided with each other and fell to the ground. The researchers found specific biomarkers that are secreted by the brain to repair nerve cell damage, but these biomarkers were not found after normal practice without hitting the ball. The researchers concluded that collisions and hitting the head with the ball lead to at least minor brain damage. The question of how harmful such injuries are is not yet answered, but it is known that repeated concussions can cause degenerative brain

disease with dementia. This issue is especially visible among boxing and ice hockey athletes.

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