Assessment of Retinal Cell Biomarkers in Experimental Model of Mild to Severe Traumatic Brain Injury Using Immunofluorescence Labeling

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ABSTRACT

Purpose: The aim of this study was to examine retinal alterations of glial fibrillary acidic protein (GFAP), SRY-box transcription factor 2 (SOX2), and thymus cell antigen 1 (THY1) in experimentally designed animal TBI models with different severity.

Materials and Methods: New Zealand rabbits were randomly distributed into four groups: control group (n = 6), mild head trauma group (n = 7), moderate head trauma group (n = 7) and severe head trauma group (n = 7). Marmarou\'s modified impact acceleration model was used to induce TBI. We examined retinal sections using immunofluorescence labeling for GFAP, SOX2 and THY1. Results: Twenty-seven rabbits (weighing 2500-3500 g at age 1–2 years) were included in the study. GFAP levels were increased in all TBI models (mild, moderate, and severe) than in the control group ($p<0.001$). GFAP level was found to be significantly higher in the severe TBI group than in the mild and moderate groups. The difference in THY1 levels was statistically significant among groups ($p<.001$). It was found that as the severity of trauma increased, THY1 levels decreased significantly between the groups. SOX2 levels were observed higher in the moderate and severe TBI groups than in the control and mild TBI groups ($p<0.001$). No significant difference was found in SOX2 levels between the control and the mild TBI groups ($p>0.05$).

Conclusion: This experimental study revealed that changes in neural biomarkers differed significantly between mild, moderate, and severe TBI groups. As trauma severity intensified, THY1 expression decreased while GFAP and SOX2 expression increased.

Keywords: glial fibrillary acidic protein, SRY-box transcription factor 2, thymus cell antigen 1, traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a critical global health challenge and can cause death or trauma-related lifelong physical and mental disability worldwide.[1] External mechanical forces induces cerebral dysfunction through both direct and indirect effects with various etiologies including car accidents, sports injuries, falls, and assaults.[2,3] TBI, with an incidence of 50 million cases per year, can be classified as mild, moderate, or severe as a result of neurological damage.[4] Mechanical damage to brain tissue and subsequent widespread neurodegeneration determine morbidity and mortality. Clinical manifestations include decreased level of consciousness, memory loss, changes in mental status, intracranial lesions and/or neurologic deficits leading to impairment in cognitive, emotional, behavioral, and sensorimotor functions, including vision.[5]

Visual impairment is a frequent consequence of TBI and often leads to significant visual impairments that negatively affect quality of life resulting in long-term sequelae.[6] The visual system is more vulnerable to the widespread effects of TBI because numerous brain pathways, cortical areas, and cranial nerves involved in vision carry sensitivity.

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Photophobia, diplopia, the blurring of vision, difficulty reading, disorders of extraocular movements and pain are among the most common symptoms of TBI related visual disturbances and affect up to 85% of subjects regardless of injury severity.[7,8] Lagged smooth pursuit movements, positional errors, and decreased acceleration in saccadic movements have been reported in patients experienced TBI.[9] Up to 90% of individuals with TBI have been reported to have oculomotor dysfunction.[10] In addition, decreased contrast sensitivity, disturbed color vision, visual field abnormalities, changes in macula and peripapillary retinal nerve fiber layer thickness detected by optical coherence tomography, and motor function disorders have been reported in association with TBI.[11–14]

TBI related neurodegeneration often results from secondary effects caused by cellular degeneration and the initiation of biochemical cascades.[15] Although retina ganglion cell (RGC) degeneration and Müller glial cell activation after TBI have been reported in rodent models in the literature,[16–18] these dynamics have been studied to a limited extent in mammals closer to human anatomy, such as rabbits.[19] The purpose of the current study was to quantitatively analyze cellular and molecular changes in retinal tissue after mild, moderate, and severe TBI in a New Zealand White rabbit experimental model using immunofluorescence labeling. The study aimed to determine the effects of the TBI severity on retinal neuronal damage, glial activation, and stem cell dynamics by evaluating the expression levels of neural stem cell proliferation, ganglion cell neurons, and Müller cell astrogliosis markers, and to compare these with a control group.

MATERIALS AND METHODS

Study Plan and Experimental Groups

New Zealand rabbits (weighing 2500-3500 g at age 1–2 years) were purchased from S***** University Experimental Medicine Research and Application Center and arrived at the facility. All subjects were housed under appropriate conditions (25 ± 2 ºC, 50% relative humidity, and a 12-h light/dark cycle) in separate cages with free access to tap water and food, and required precautions were taken during the study to minimize pain and stress associated with experimental interventions. The National Institutes of Health Guide for Care and Use of Laboratory Animals was adhered to all experimental procedures. The study protocol was approved by the Local Ethics Committee for the S***** University Experimental Medicine Research and Application Center (Protocol No:2026/35).

Twenty-seven New Zealand rabbits were subjected for the experimental procedures. The required number of animals was determined using the Mead's Resource Equation method.[20-22] Rabbits were randomly distributed into four groups: control group (n = 6), mild head trauma group (n = 7), moderate head trauma group (n = 7) and severe head trauma group (n = 7). Marmarou's modified impact acceleration model was used to create a head trauma model in rabbits (Figure 1).[23] Anesthesia was achieved by administering 40 mg/kg ketamine and 10 mg/kg xylazine hydrochloride intramuscularly into the hind leg to each rabbit. The impact acceleration model (organized by H.K. and İ.Ş) was placed on a flat platform with the sedated rabbits in a prone position. To create diffuse damage from the falling weight and to provide a larger cranial contact surface, a midline scalp incision was made under sterile conditions, and a stainless-steel metal disc was placed between the coronal and lambdoid sutures at the vertex of the rabbits. During the experiment, metal balls weighing 200 gr for mild head trauma, 350 gr for moderate head trauma, and 500 gr for severe head trauma were dropped from a 1-meter-long tube system onto the metal disc placed on the rabbits' skulls by gravity. In the post-traumatic period, intravenous paracetamol (7.5 mg/kg) was ordered once every 6 hours to minimize pain until sacrifice. Rabbits in the control group (n=6) were not subjected to trauma. After 24 hours, all subjects survived and were all sacrificed at the same point with 80 mg/kg ketamine. Globes were taken and examined to immunohistochemical analysis following the sacrifice.

Histological Analysis

Histological examinations and measurements of the tissues were performed in the Departments of Histology and Embryology of Medical Faculty at S***** University. The eye tissues were obtained and fixed in freshly prepared and chilled 4% paraformaldehyde in PBS for 24 hours at a temperature of +4 °C. After fixation, the tissues were immersed in a 30% sucrose solution at a temperature of +4 °C for one night. Sections were cut from the globe using a cryostat device (Leica RM2125 RT) with a thickness of 5

µm at a temperature of −25 °C and then placed onto poly-L-lysine slides. The sections were incubated with primary antibodies for glial fibrillary acidic protein (GFAP), SRY-box transcription factor 2 (SOX2) and thymus cell antigen 1 (THY1). Labeling was performed with secondary antibodies (Alexa Fluor 488/555/647). Nuclear staining was achieved with DAPI. Imaging was obtained with An Olympus BX51 trinocular fluorescence microscope. A DP72 camera with a 40× objective magnification was utilized to take digital images of six random retinal regions. Fluorescence intensity for each marker was quantitatively evaluated using ImageJ software (National Institutes of Health, Bethesda, Maryland, USA). The immunofluorescence signals were independently evaluated by two experienced observers who were blinded to the study groups. Fluorescence intensities were compared between groups for each marker.

Statistical Analysis

All statistical analysis was performed using R (version 4.5.2, www.r-project.org) Statistical Computing. Data were expressed as mean ± standard error of the mean. The Shapiro–Wilk normality test was applied. To assess the difference between experimental study groups, we conducted the one-way analysis of variance (ANOVA), followed by independent t-test with false discovery rate (FDR) correction for pairwise comparisons. FDR correction was opted to be able to trust all the significant results where sample sizes were limited relative to the number of tests. A p-value less than 0.05 was considered as statistically significant.

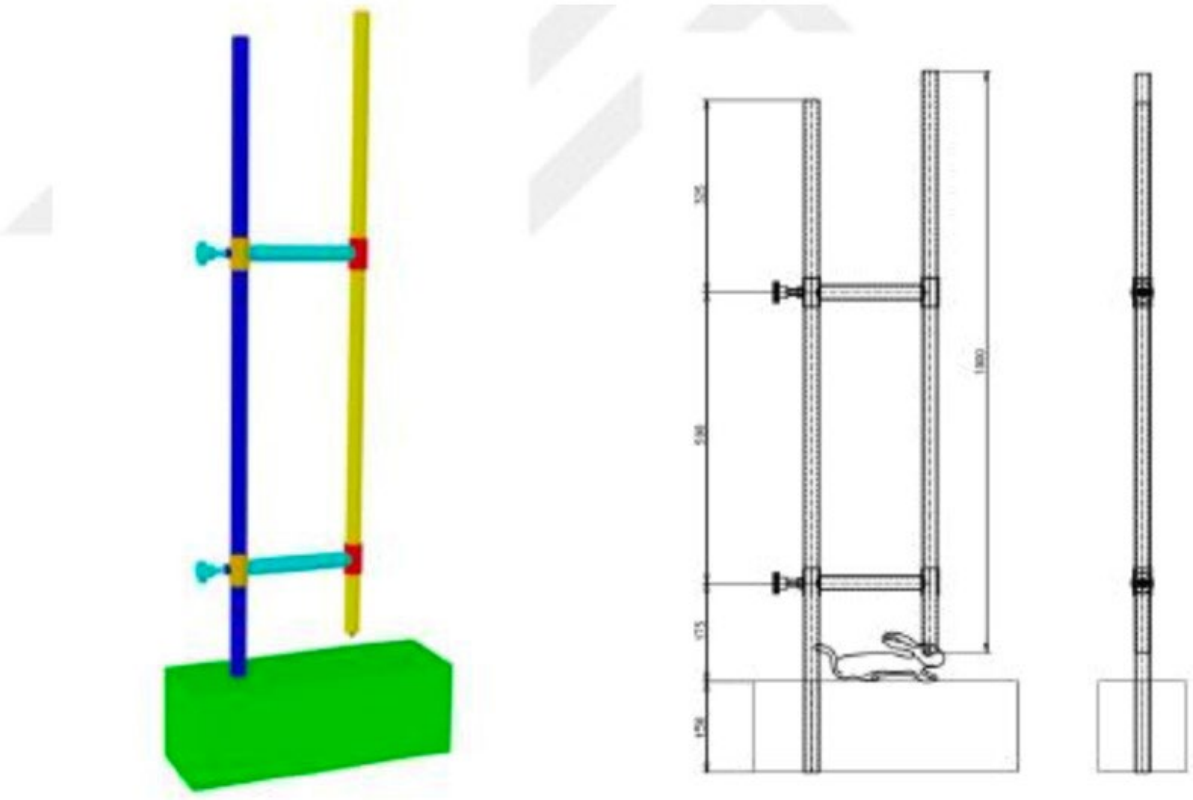

Figure 1: *Schematic representation of the Modified Marmarou impact acceleration model. Left; three-dimensional isometric view of the device; consisting of two vertical bars (blue and yellow) mounted on a green base and two horizontal bars connecting them, adjustable in height by screw mechanisms. Right; Front and side technical drawings of the same setup, with relevant dimensions (in mm): base height ~156 mm, height of the lower horizontal bar above the base ~175 mm, distance between the two horizontal bars ~598 mm, free section above the upper horizontal bar ~525 mm.*

RESULTS

Histological staining for all subject groups is demonstrated in Figure 2. Significant differences among experimental groups for all antibodies were found by one-way ANOVA (Table 1 and Figure 3). Levels of GFAP were also significantly different among the groups (F=22.066, p<0.001). Post-hoc tests revealed a stepwise rise in the levels of GFAP, and the levels in the severe trauma group were considerably increased compared to the levels in the other groups. In addition, the levels in the mild and moderate trauma groups were considerably increased compared to those in the control group, with no significant difference noted in the mild and moderate trauma (Figure 3A).

Moreover, the expression level of SOX2 exhibited a significant difference among the groups (F=28.652, p<.001). There were no significant differences between control and mild trauma groups. Conversely, there were significant differences in the expression levels of SOX2 in both moderate and severe trauma groups compared to control and mild trauma groups (Figure 3B).

The difference in THY1 levels was significant among groups (F=18.055, p<.001). However, it was noted that, in contrast to GFAP and SOX2 expression, THY1 expression decreased as trauma increased. The control group values were significantly higher than those of the trauma groups. The mild trauma group had intermediate values. The lowest values were those of the moderate trauma and severe trauma (Figure 3C).

Table 1: *Comparison of antibodies among experimental study groups*

Antibodies	Control Group	Mild Trauma Group	Moderate Trauma Group	Severe Trauma Group	Test statistics and *p*-value
GFAP	2.510 ± 0.182^{a}	3.792 ± 0.300^{b}	4.101 ± 0.271^{b}	6.367 ± 0.520^{c}	F=22.066, p<0.001
SOX2	2.653 ± 0.330^{c}	2.151 ± 0.259^{c}	7.765 ± 0.714^{b}	8.536 ± 0.933^{b}	F=28.652, p<0.001
THY1	7.371 ± 0.771^{a}	4.742 ± 0.526^{b}	2.925 ± 0.469^{c}	2.220 ± 0.280^{c}	F=18.055, p<0.001

Different small superscript letters indicate statistically significant differences after multiple comparisons. Test statistical and *p*-value obtained by one-way ANOVA. Abbreviations: GFAP, glial fibrillary acidic protein; THY1, Thymus cell antigen 1; SOX2, SRY-box transcription factor 2.

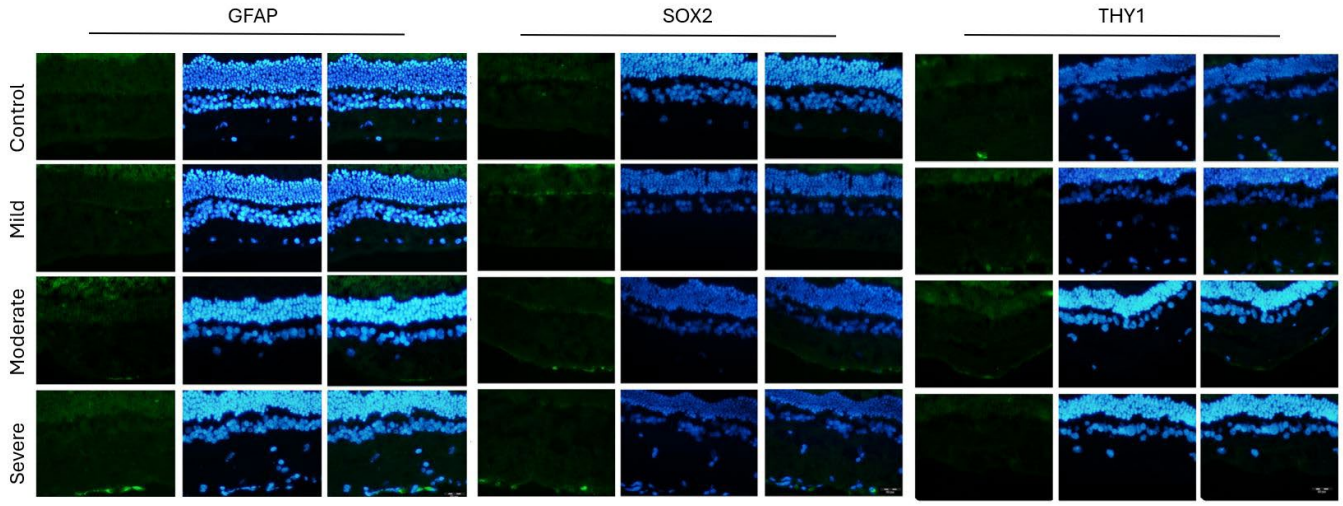

Figure 2: *The expression of glial fibrillary acidic protein (GFAP), SRY-box transcription factor 2 (SOX2) and thymus cell antigen 1 (THY1) in the retinal sections of control, mild, moderate, and severe traumatic brain injury in rabbit experimental model using immunofluorescence labelling (green) and the nuclear marker DAPI (blue). The first column in the groups shows images with antibody and immunofluorescence labeling for GFAP/SOX2/THY1. The second image in the middle is nuclear staining with DAPI. The third image is a combination of the first two images. Scale bar slots in the images are 20 µm.*

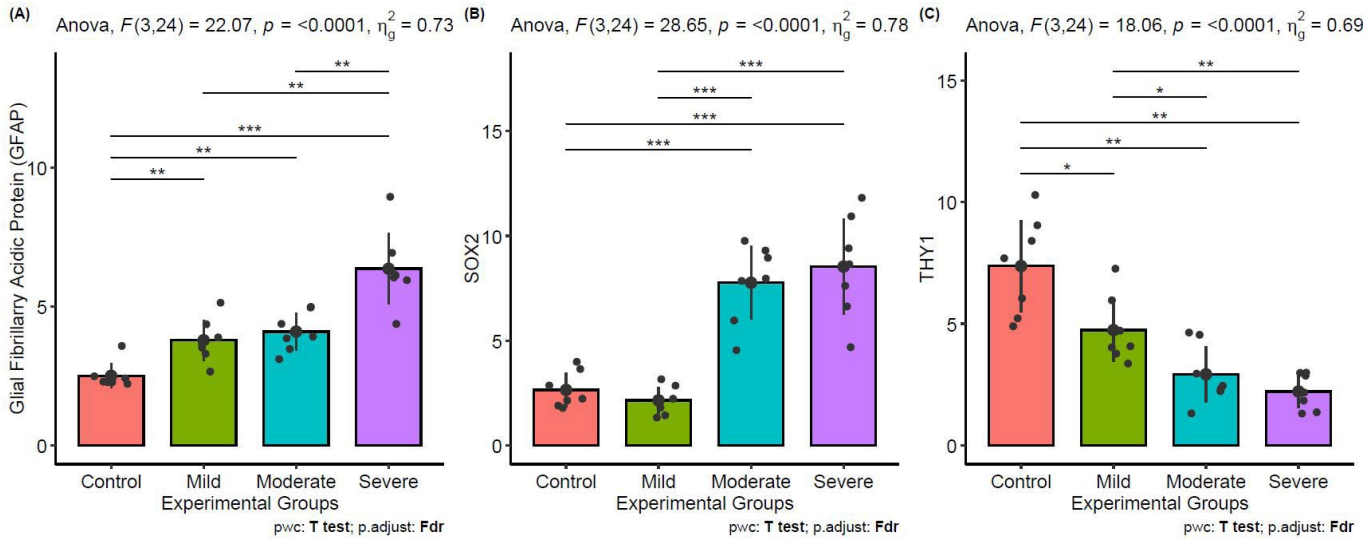

Figure 3: *The error-bar plots of experimental groups in (A) GFAP, (B) SOX2, and (C) THY1 levels. Data was presented as mean ± SEM. One-Way ANOVA was used for comparison of groups, and multiple comparisons were performed using FDR-adjusted post-hoc independent t-test. Horizontal lines indicate statistically significant pairwise differences (*p<0.05,**p<0.01,***p<0.001).*

DISCUSSION

This study demonstrates that TBI model with three different intensities induce astroglia cell activation, inflammation, immune dysregulation and neuronal loss. It was aimed to elucidate the diffuse effects of TBI on the visual system and identify biomarkers for early inflammation and novel targets for therapeutic interventions. Blood-brain barrier disruption, inflammatory processes, formation of free radicals, cytotoxicity due to release of the excitatory neurotransmitter glutamate, influx of calcium and sodium ions into neurons and mitochondrial dysfunction can damage neurons and lead to neuronal loss because of TBI.[24] Severity classification of TBI is determined by clinical assessment grading scores based on the Glasgow Coma Scale, which classifies TBI as mild (14–15), moderate (9–13), or severe (3–8).[25,26] It has been reported that neuro-ophthalmological changes can occur after TBI, which may also be present in most patients hospitalized for ocular trauma.[27] Our study showed an increase in GFAP and SOX2 and a decrease in THY1 in retinal tissue sections after TBI, demonstrating that neuronal damage can occur in the eye as well as in the CNS. Furthermore, the current study revealed that traumatic effects on the retina could be encountered in all models of TBI, from mild to severe.

Astroglia cell activation (astrogliosis) is a complex protective response of the central nervous system (CNS) to damage to neurons due to injury, infection, stroke, or neurodegenerative diseases, in which astrocytes exhibit abnormal proliferation, growth, and molecular changes. GFAP, is an intermediate filament-III protein in astrocytes, is increased in astrogliosis following CNS injuries and neurodegeneration.[28] GFAP has been considered as a protein biomarker for neurotrauma and stroke.[29] Immunofluorescence analysis of GFAP can be used to evaluate local tissue inflammation and neurodegeneration. In the present study, GFAP levels increased in all trauma groups compared to the control. This increase was observed most prominently in the severe head trauma group. In an experimental porcine model of TBI, plasma levels of circulating GFAP were found to be elevated.[30] However, the source of the increase in GFAP detected in plasma was unknown. On the other hand, we demonstrated the increase in GFAP directly in retinal sections after TBI. The current study has shown that the optic nerve and retina are directly connected to the CNS and are affected following TBI. Evanson et al. reported increased GFAP staining in these optic tract, lateral geniculate, and superior colliculus seven days after the neuro-injury in a murine TBI model.[31] Even if neuroimaging was normal, they showed increased GFAP levels in subjects who had sustained mild TBI, indicating the development of traumatic optic neuropathy (TON). Similarly, we detected an increase in GFAP staining in all TBI groups in our study. Although GFAP levels did

not differ between mild and moderate TBI, the increase observed even in the mild TBI group indicates that the visual system was clearly affected by TBI. Compared to mild and moderate TBI, the greater increase in GFAP is reasonable in the severe TBI group. Even the increase in the mild traumatic brain injury group demonstrates that every case following TBI should be evaluated neuro-ophthalmologically and examined for the development of TON.

SOX2 is one of the critical transcription factors for maintaining self-renewal and regulating brain development and neurogenesis.[32] It is an oncoprotein found in neural stem cells that maintains the undifferentiated state of cells. SOX2-expressing cells are multipotent and capable of self-renewal in the adult neurogenic environment. They are generally quiescent but can be activated by injury or growth stimulation. Studies have shown that reducing the expression of the SOX2 gene in astrocytes, which are activated in response to post-traumatic injury, can reduce glial scarring, decrease cell loss in the cortex, and significantly improve behavioral recovery.[33,34] In our moderate and severe TBI model, we observed an increase in SOX2 positivity. The similarity of SOX2 levels between mild trauma group and the control group may suggest that the prognosis would be better compared to the moderate and severe trauma groups. We demonstrated that post-traumatic injury may be more prominent in moderate and severe TBI groups through differences in SOX2 levels compared to mild TBI group. Higher SOX2 expression was thought to be associated with poor prognosis.

THY1, is a cell surface glycoprotein marker, provides cell proliferation and communication in numerous cell types, especially in cells of nervous system and is mainly expressed by the RGC within the retina.[35] Its deficiency is associated with impaired healing and altered cell/matrix interactions. It has been shown that Thy1 levels decrease after damage to the optic nerve and retina, and this is associated with RGC loss in the affected areas. It is thought that the downregulation of THY1 precedes a designated step in the apoptotic program. Immunohistochemical measurement of retinal Thy-1 mRNA levels was reported as a useful method for detecting RGC death.[32] In our study, THY1 was reduced in all TBI models compared to the control group. It was thought that the decreasing THY1 as the intensity of trauma increased indicated RGC loss. Similarly, Struebing et al. observed higher expression of THY1 after ocular blast injury model in the mouse retina.[36] They found that the decrease in Thy1-cyan fluorescent protein-positive RGCs identified the cause of ongoing vision loss. In another experimental study conducted with Thy1-Cyan fluorescent protein mice model, multiple repeated brimonidine treatments slowed the initial rate of RGC loss after optic nerve crush.[37] Our study concluded that a decrease in THY1 could be associated with RGC loss and correlated to the severity of trauma.

Retina has potential as a non-invasive window into the molecular pathophysiology of TBI. Cellular biomarkers such as ionized calcium-binding adapter molecule 1, GFAP, phosphorylated tau and various cytokines (IL-1β, IL-6, and TNF) have emerged as direct indicators of brain health and TBI severity in the light of the recent studies.[38] Based on the results of our experimental model, SOX2 and THY1 were also involved in inflammatory responses and neurodegenerative processes related to TBI severity as well as GFAP. The research we presented has a few limitations. We did not use subjects in different age groups, which may have different results. Another limitation of the current study was that our experimental model potentially mimics TBI with different severities, but it may not be applicable to TBI developing due to different causes such as car accidents, sports injuries, falls, and assaults. The future studies will focus on understanding the brain–retina relations after TBI and provide practical contributions to clinical applications (e.g., ophthalmological screening protocols, neuroprotective treatments) and neurorehabilitation.

CONCLUSION

The regenerative potential of neural biomarkers offers a basis for neuroprotective therapies, while neuronal loss and glial activation markers will reveal the mechanisms of vision loss and inflammatory responses. Neuro-ophthalmic manifestations of TBI are often underdiagnosed and can occur regardless of the severity of the trauma, leading to late presentation with permanent visual impairment and visual field defects. The necessity of routine eye examinations in both the acute and chronic phases of TBI is an undeniable fact.

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