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RESEARCH ARTICLE

IDENTIFICATION OF NEW BIOMARKERS AND PROMISING NEURO IMAGING OF DIFFUSE AXONAL INJURY: AN OBSERVATIONAL STUDY

Sanjay Kumar Mishra[1], Sushant Agarwal[2], Bikash Agarwal[3], Vikas Shrivastava[4], Vibha Kumari[5], Gaurav Dubey[6], Jyoti Bhushan Babbar[7] and Mayadhar Barik[8]

1. Scientist, Dr. R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences (AIIMS), New Delhi, India.
2. Assistant Professor of Radiology Gauhati Medical College & Hospital, Guwahati, Assam, India.
3. Adv. Anaesthesiology, Command Hospital, Lucknow, Uttar Pradesh, India.
4. Professor, Department of Paramedical and Allied Health Sciences, Division of Optometry, Galgotias University, Uttar Pradesh, India.
5. Assistant Professor, Department of Paramedical Sciences, School of Nursing Sciences & Allied Health, Jamia Hamdard, New Delhi, India.
6. Resident, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India.
7. Associate Professor in the department of Community Medicine, NIIMS, Noida, India.
8. Professor and Head, Department of Paramedical & Allied Health Sciences, Biochemistry, Mewar University, NH-79, Gangrar, Chittorgarh Rajasthan, 312901, India.

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Abstract

Objective: To determine the clinical patterns of the newly identified novel biomarkers of prognosis among adult patients with traumatic brain injury (TBI), diffuse axonal injury (DAI) and ophthalmic injury (OI) and micro bleeds in the Brain.

Methods: According to the online search engine from the databases of PubMed, Embase, Ovid Science Direct, and the way of sciences of the original contribution articles which are providing with the essential information about outcome in patients with DAI in general, DAI vs. non-DAI, related to magnetic resonance imaging (MRI) classification , related to lesion and their specific , Specific location/load and their future outcomes. We have gone through the major references and checked their quality control (QC) assessments performed through International standard protocol/guidelines and our own experiences.

Results: A total of 585 articles were included. TBI patients with DAI patient's favorable outcomes are (75-90 %). The risk associated unfavorable outcome (RAUO) is in TBI with DAI was three to four times higher than in TBI without DAI in our Asian Indian patients.The Odds ratio (OR) for their unfavorable outcome was 2.7 as per increase of DAI grade on the MRI findings. Lesions are located in the area of the corpus callosum (CC) associated with an unfavorable outcomes reported frequently (85-95%).

Conclusions: DAI patient's management through MRI and patients with with TBI results unfavorable outcome are increasing in larger in numbers day by day in trauma care. MRI grading, locations, pattern of

Corresponding Author:- Prof. (Dr.) Mayadhar Barik
Address:- Professor and Head, Department in the Paramedical & Applied Sciences, Biochemistry, Mewar University, NH-79, Gangrar, Chittorgarh, Rajasthan, 312901, India.

diffuse (POD) and axonal injury rates (AIR) are increasing in their three to four fold with every grade. Associated Lesions in the corpus callosum (CC) are associated with an unfavorable outcomes are those frequently associated with the DAI patients in TBI. Need appropriate diagnosis and management for DAI. Our newly developed biomarkers are quite useful for DAI patients associated within the TBI patient's management and follow-up.

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Introduction:-

The longitudinal cohort population research (LCPR) in the clinical evidence of DAI on MRI findings may be one the best useful for predicting the short-term observation in-hospital[1].The prognostic impact of magnetic resonance imaging (MRI)-defined diffuse axonal injury (DAI) after traumatic brain injury (TBI),microbleeds on functional outcomes, quality of life (QOL) and their mortality are 3-5 year are associated in DAI patients reported globally[2]. DAI patients with and their long-term TBI outcomes, providers a cautious attribution in the DAI patients future neurologic function (FNF), quality of life (QOL) and/or survival rate [3-4].

DAI and long-term TBI patients were cautious to attribute in DAI to future neurologic function, quality of life (QOL), survival and their physical life (SPL)[5-6].Traumatic brain injury (TBI) is basically associated with elevated rates of neurodegenerative diseases such as Alzheimer's & parkinsonism disease (PD). As the chronic traumatic encephalopathy (CTE) diseases are more important[7]. Diffuse axonal injury (DAI) triggers up the post-traumatic neurodegeneration (PTND), with axonal damage (AD) leading to the Wallerian degeneration (WD) [8]. The toxic proteinopathies of amyloids and the hyperphosphorylation of the tau protein alteration also one causal factor of these diseases, but it is not clearly discussed/mentioned by the literature [8]. The prognostic accuracy is quite helpful to identify the patients those are in greatest neurodegenerative risk (GNDR) for inclusion in clinical treatment trials in their respective institutions, hospitals and the research center [9].Traumatic brain injuries (TBIs) are grouped by their severity in the **(poor, mild, moderate and severe)** clinically. The Mild TBI in the least of their severe form is synonymous with the blunt non-penetrating head trauma (BNPHT) is also very important to know DAI [10].

The traumatic brain injury (TBI) is causes in the stretching and tearing of axons (TOA) is one leading into the diffuse axonal injury (DAI). According to the clinical & pathogenetic mechanism of this disorder is located routinely in the TBI patients [11]. However, in the mild TBI clinical grounds if we observe not a single well-validated imaging (WVI) or fluid biomarkers (FBs) to determine the presence of severity of neuronal damage (SOND) at axon in DAI patients with mild TBI till date [12]. DAI patients with mild TBI patients were recovering and others report persistent symptoms, called post-concussive syndrome (PCS) is another critical conditions underlying pathophysiology of which is largely unknown in diffuse axonal injury (DAI). [13].

In addition to the repeated concussive and subconcussive head injuries (RCSHI) have been linked to the neurodegenerative conditions are varies according to their clinical conditions [14]. The chronic traumatic encephalopathy (CTE) is reported by the post-mortem in contact sports athletes and soldiers exposed to blasts in the earlier study [15].

CTE plausibly shed lighting on the underlying cellular and molecular processes involved in mild TBI is insights from of the severe injuries in patients with DAI [16]. MRI techniques in NMR, Radiology and Nuclear Medicine, and blood tests for the axonal proteins are need to identify by the young scientist and gradation will be define according to severity of the axonal injury is helpful for the management of patients with the DAI [17]. **I**n addition to PET scan for the tau pathology promises into as newly discovered tools to explore CTE pathophysiology in longitudinal clinical studies for DAI patients in our specific observations [18], CTE pathophysiology might be able to develop a better diagnostic tools for CTE in DAI with TBI patients [19]. CTE is attributing to repeat the head trauma injury (HTI) , axonal injury (AI) is for prevention is one new possible direction through this new rule in changes by the sports organizations and legislators for the better diagnostic tools for the appropriate CTE in DAI including with the TBI patients [20].

Materials and Methods:-

Sample collections:

This is a retrospective cohort study included adult trauma patients (age > 17 years) admitted and repots were observed from 1985 to 2022 with DAI including with the TBI patients in DAI. We also considered both male and female. **Selection Criteria:**

Inclusion criteria:

Inclusion criteria were positive head computed tomography with brain MRI within admission patients report with imaging subject and patients DAI including with the TBI patients.

Exclusion criteria:

Exclusion criteria included penetrating to those are not associated with the TBI or prior to the neurologic other several types of the clinical conditions not associated with DAI patients are excluded from this study.

Methods:-

Online search engine in (PubMed, Embase, Ovid Science Direct, and the way of sciences) of the original contribution articles providing the essential information about outcome in patients with DAI in general, DAI vs. non-DAI, related to magnetic resonance imaging (MRI) classification and related to lesion and their specific, Specific location/load and outcomes. We include the Separate ordinal logistic models (SOLMs) to assessed DAI's prognostic value for the following scores in the major issues unlike hospital-discharge Functional Independence Measure, long-term Glasgow Outcome Scale-Extended, long-term Quality of Life and there after the Brain Injury-Overall Scale Index (BIOSI). As per the MRI (Y/N), research-level anatomic DAI Grades I-III in I, cortical; II, corpus callosum; III, brainstem, ventilator days, time to follow commands, and time to long-term follow-up care is important for logistic models were selectively performed.

Statistical analysis:

Cox proportional hazards modeling assessed DAI's prognostic value for 3- 5 year survival. Covariates included age, sex, race, insurance status, Injury Severity Score, admission Glasgow Coma Scale Score, Marshall Head computed tomography Class, clinical DAI on MRI (Y/N), research-level anatomic DAI Grades I-III (I, cortical; II, corpus callosum; III, brainstem, ventilator days, time to follow commands, and time to the long-term follow-up care) and their impact in percentages are taken.

Results:-

Currently, perinatal care emerging (PCE) over the period of the past twenty years have helped to diminish the mortality and severe neurological morbidity & co-morbidity[21]. As of extremely and very preterm neonates are the cystic Periventricular Leukomalacia [c-PVL] and Germinal Matrix Hemorrhage - Intraventricular Hemorrhage [GMH-IVH grade 3-4/4][22].We have observed that 38 to < 42 weeks of gestational age is also important for the premature [23].The motor and/or cognitive disabilities associated with the mild-to-moderate findings in the white gray matter injury (WGMI) are present in DAI patients with TBI is more than 90% [24]. In this population we noticed that non-cystic Periventricular Leukomalacia [non-cystic PVL], The neuronal-axonal injury (NAI) and GMH-IVH grade 1-2/4) are also associated in DAI patients frequently [25]. According to our observations in the Brain research studies the magnetic resonance imaging (MRI) findings reporting that 85% to 90% of extremely diffuse locations part [26]. The majority of preterm neonates have diffuse white matter abnormalities (WMAs) are quite less [27]. As it corresponds to the minimum grade of severity level only [28].

Although, the mild-to-moderate diffuse WMA is also associated with significant affectations at the motor and cognitive activities [29-30-31]. Neonatal survival is increased due to the intrinsic characteristics of diffuse WMA [31]. There is an acute growing need to study the brain structure and function of the premature infant using by the non-invasive neuroimaging techniques **(NINITs)** sensitive to microscopic and their diffuse lesions carefully [32]. This emerging need has led the scientific community to try to maintain the bridge between the gap concepts or ideas from the different methodologies and several bias approaches [33]. The correct decision is required for instance; neuropathology, neuroimaging and clinical findings and suitable guideline are still required for DAI patients in India [34-35]. According to the combination of the intense pre-clinical and clinicopathologic research along with neonatal neurology and quantitative neuroimaging research is required for the more further improvement [36-37]. Here, we explore that newly discovered Biomarkers in the brain & Eye literature relating to

neuropathological patterns with the recent neuroimaging findings in preterm newborns and infants with perinatal brain injury (PBI),DAI,TBI, HTI research and appropriate findings are needful [38-39-40]. According to our special observation attached here with Table no:1 (**IDENTIFICATION OF NEWLY DISCOVERED DAI in TBI IN THE BRAIN & EYE BIOMARKERS").**

Discussion:-

In humans the link between diffuse axonal injury (DAI) and subsequent neuro degeneration process has yet to establish [51].As per the earlier research hypothesis that the severity and location of predicts degree of the progressive post-traumatic neuro degeneration (PPTND) in the DAI [52]. DAI patients within the chronic phase after moderate-severe traumatic brain injury (TBI) and the healthy control subjects [53]. Fractional anisotropy (FA) calculated from diffusion tensor imaging (DTI) to measure the DAI [54].

Jacobian determinant atrophy (JDA) rates were calculated from their serial volumetric T1 scans (SVT1) as an apparent measurement in the post-traumatic neurodegeneration (PTND) are more than 85-90% [55-56]. The minimum range of potential predictors of longitudinal post-traumatic neurodegeneration (LPTND) is compared the variance in brain atrophy (BA) is more than 95% quite important for the management & research [57-58].

DAI evidence and reductions of fractional anisotropy (FA), (BA) is also given the clear picture to know the better diseases progression [59]. The baseline characteristic and patients care follow –up and follow-up in imaging parts of the white matter very essential part to verify and patient's management [60]. Although there is no significant changes in fractional anisotropy (FA) over time (FA), (BA) are varies in DAI [61]. The brain atrophy abnormality (BAA) rates are pretty high in the both of the grey and white matter (GWM) in DAI patients [62]. DAI location and extent of diffuse (EOD) in axonal injury predicted through the degree of brain atrophy (BA) , fractional anisotropy (FA) predicted progressive brain atrophy (PBA) in both the whole-brain and voxelwise analyses are more useful [63]. The strongest relationships are observed in the DAI is the central white matter tracts (CWMTs) and the body of the corpus callosum (CC) is more than (95%) [64]. DAI predicted more variability in white matter atrophy (WMA) than other putative clinical imaging measures more than 90% [65].DAI includes the baseline brain volume (BBV) , age, sex, clinical measures, axonal injury severity(AIS) and microbleeds (>50% for fractional anisotropy (FA) versus <5% for other variations measures are also important for the DAI management and the TBI research [66].

Conclusions:-

Newly discovered biomarkers quite helpful to analyze the shear axonal injuries (SAI), functional impairment (FI), axons injury (AI) and decreased blood flow (DBF) and their abnormal metabolic activity (AMA) in the brain parts affected with DAI. The multimodal MRI approach in patients with DAI results is differencing representation in the underlying pathophysiological changes of the severe damage injured nerve tracts (SDINTs). MRI findings are helping to improve the diagnostic and prognostic accuracy of the MRI in DAI. T2*-weighted gradient-echo imaging also shown at higher level field strength and very useful tool for the evaluation process of the DAI patients during the chronic stage of traumatic brain injury (TBI).

Table No 1:- (Identification Of Newly Discovered Dai In Tbi In The Brain & Eye Biomarkers).

SlNo:	**Organelles : For accurate diagnosis and prognostic prediction**	**NEWLY DISCOVERED DAI IN EYE BIOMARKERS**	**Impact**	**Remarks**
1.	Consciousness level and recovery outcome in ABI	Regions and networks	Intrinsic functional connectivity strength (IFCS) of whole-brain networks	Using resting-state fMR
2.	Early prevention and control of high myopia.	Serum metabolomics profiling	Pathophysiological changes and pathogenesis of myopia	Liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF/MS)

3.	Age-related macular degeneration (AMD)	Investigating regional distribution of FV in the CC	Analysis of regions of CC FV around GA margins	OCT angiography (OCTA), swept-source OCTA (SS-OCTA)
4.	Glaucoma and other optic neuropathies	Nerve fiber layer	Dysfunction and loss of retinal ganglion cells and their axons	The development of novel biomarkers for glaucoma in the context of disease pathophysiology
5.	Traumatic Brain Injury	Serum levels of G-CSF,	Higher G-CSF levels in severe TBI	Peripheral leukocyte and neutrophil counts at different time points
6.	severe TBI (STBI)	Tumor necrosis factor-α (TNF-α) inflammatory biomarkers	Different pattern from those in the mild and moderate TBI groups	Peripheral leukocyte and neutrophil counts at different time points
7.	Traumatic brain injuries (TBIs)	Glasgow Coma Scale (GCS)	Motor, eye, and verbal responses to evaluate the level of consciousness of the patient	Injuries are classified as mild, moderate, or severe depending on the GCS score
8.	Traumatic brain injuries (TBIs)	S100 calcium-binding protein B (S100B	GFAP and MRI in TBI	Molecular test
9.	Traumatic brain injuries (TBIs)	Glial Fibrillary Acidic Protein (GFAP; 5 Studies)	GFAP and MRI in TBI	Molecular test
10.	Diffusion-weighted imaging (DWI).	Diagnosis of DAI	Fractional anisotropy changes and DAI reflect	MRI Technique
11.	mTBI	MRI-Based TBI Diagnosis and Rationale for Serum Biomarker	Post-traumatic lesions except for acute fractures or hemorrhage,	MRI Technique

NB: acquired brain injury (ABI), Age-related macular degeneration (AMD), OCT angiography (OCTA), swept-source OCTA (SS-OCTA) , severe TBI (STBI), diffusion-weighted imaging (DWI).

Specifically, DAI patients reports are the use of neuroimaging to aid diagnosis [41], measured through the morphometric brain damage (MBD), their long-term neurodevelopmental (LTND) outcomes track are increasing [41-42]. Lesions are located in the area of the corpus callosum (CC) locations associated with an unfavorable outcomes reported frequently (85-95%) of the patients. The T2*-weighted gradient-echo imaging revealed that traumatic microbleeds (TMBs) rate are increasing in DAI [43]. Hyperintense foci (HIF) rate observed on the T2-weighted images of only patients are (20-25%) [43-44]]. T2*-weighted imaging explained more in traumatic microbleeds (TMBs) (P =.001) than did T1- and T2-weighted imaging significantly [45]. According to the statistical findings an Inter observer agreement pattern (IAP) stronger than the values of (kappa = 0.80, tau = 0.745, P =.001). (20-30%) of the patients with DAI well defined according to the STRATA new version [46], T2*-weighted gradient-echo imaging shown (75-90%) traumatic microbleeds in the corpus callosum area [47], Here hyperintensecallosal lesions were seen on the T2-weighted images are (3- 5%)[48]. Hence a significant correlation existed between the total amount of the callosal appearance in the traumatic microbleeds Injury [49]. As per the Glasgow Coma Scale scores (GCSS) (P =.001). So we here mentioned that there is no correlation between the existed & non-existed extended with then the Glasgow Outcome Scale scores (GOSS) 90-95% [50].

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