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CEREBRAL MICROHEMORRHAGES DUE TO TRAUMATIC CEREBRAL INJURY AND THEIR EFFECTS UPON THE AGEING HUMAN'S CEREBRUM

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ABSTRACT
Cerebral microbleeds are frequently associated with traumatic cerebral injury, their effects upon clinical outcome after traumatic cerebral injury continue debatable and poorly-understood, predominantly in older citizens. Here we, (A) high spot main challenges and changes associated with studying the effects of traumatic cerebral injury - mediated cerebral microbleeds. (B) Review the indication of their possible effects upon perceptive and neural outcome as a purpose of age at injury, and (C) recommend priorities for future investigation on understanding the clinical suggestions of cerebral microbleeds. While traumatic cerebral injury mediated cerebral microbleeds are likely different from those due to cerebral amyloid angiopathy or to other neurodegenerative illnesses, the effects of these two cerebral microbleeds types upon cerebral function may share mutual topographies. Also, in older traumatic cerebral injury fatalities, the incidence of traumatic cerebral injury mediated cerebral microbleeds may estimate that of cerebral amyloid angiopathy associated cerebral microbleeds and thus permits a thorough study. Because the modifications effected by cerebral microbleeds upon cerebral structure and role are both inimitable and age reliant on, it looks likely that novel, age-tailored healing approaches are essential for the proper clinical clarification and management of these omnipresent and underappreciated traumatic cerebral injury sequelae.

KEYWORDS: Traumatic cerebral injury(TCI), Cerebral microhemorrhages (or microbleeds, CMBs), cerebral amyloid angiopathy(CAA), traumatic axonal injury (TAI), blood-brain barrier (BBB), mild TCI (mTCI), susceptibility weighted imaging (SWI), magnetic resonance imaging (MRI).

INTRODUCTION
TCI is a severe disorder with significant epidemiological and clinical consequence. The neural and perceptive significances of TCI can be severe irrespective of the patient's age at injury, though sequelae are chiefly devastating in elder patients. For demonstration, TCIs occur in over 5% of persons over the age of 60 and rely far on superior morbidity and mortality in this age group than in younger cohorts. Even after regulating for injury type and austerity, every span of life increases the likelihood of poor clinical outcome after TCI by as much as ~50% and elder patients are significantly more likely to die from TCI than younger victims. TCI also fast-tracks cerebral ageing and the ruin of neural function with an average difference between survivor's linear age and their biological cerebral age of five years. Moreover, a recent detailed study of nearly 14,000 patients recommended that TCI rise the pathogenic hazard ratio for neurodegenerative illnesses by a factor >3.[1-3]

CMBs organise an abundant indicator of TCIs of all severities, and their incidence is sturdily related to that of TAI. It was indicated that 45% of patients dying in the acute phase of TCI and 48% of those who survive TCIs to live for one year or more, displaying multifocal, perivascular and parenchymal CMBs in the grey matter. Where (A) long-range axonal connections dismiss and (B) cerebral tissue was subjected to a substantial gradient of physical momentum in traumatic tests. Mounting indication recommends that CMBs be implicated in the pathogenesis of CAA an increasingly reinforced suggestion whose potential implications are mirrored by epidemiological conclusions to the effect that CMB incidence may raise dementia risk by a matter of at least 1.8. A mild TCI (mTCI) survivors who display CMBs during the acute stage of grievance are 1.6 times more likely to suffer from Parkinson's disease, and their death rate is much advanced than that of the overall populace, with an associated HR of 1.7.[1,4,5] This review portrays the cellular mechanisms and potential significances of CMBs during the condition or process of deterioration with age and recommends paths for future review within this significant yet underprioritized field of analysis. The tasks of defining the extent to which the CMBs of older TCI sufferers are related to either TAI or CAA were emphasised, and potential approaches for answering this vital query are anticipated. Based on present evidence, we contend that, in older hosts, the incidence of TAI-

mediated CMBs can be similar to that of CAA associated CMBs and may, therefore, be essential for the detailed study in future. Here and all over, TBI intermediated CMBs refer to white matter injuries or, more exactly to SWI detectable white matter hypo intensities related to CMBs after TCI.

Procedures of CMB incidence

Intracerebral haemorrhage was known to the world on an early 17th century when Johann Jacob Wepfer (1620–1695) found fragile vessels in relative to a sizeable cerebral haemorrhage but was unable to recognise a point of estrangement. In 1868, Charcot and Bouchard analysed the content of microaneurysms, and the impact of CMBs became even more extensively approved once Ramon y Cajal was described the neurotoxic effects of blood extravasation on early 1928s. Among these effects the occurrence of neural tissue necrosis, which takes in the death of neural cells, whose severity increases significantly as the cerebrum ages and whose sequelae last longer as the efficacy of neural repair mechanisms drops. The development of CMBs is supposed to include diapedesis, whereby erythrocytes rapidly cross the endothelium of the BBB to form hemosiderin then ferritin deposits within petechiae of the cerebral parenchyma. The time rate of diapedesis is strongly reliant upon BBB permeability, which is characteristically higher in males begins to increase radically after age 44 and maybe two to three times higher after age 60 compared to age 30. Thus, the higher permeability of the BBB in older TCI patients has long been accepted as a significant factor providing to the severity of post-injury cerebrum tissue injury.[2,6,7]

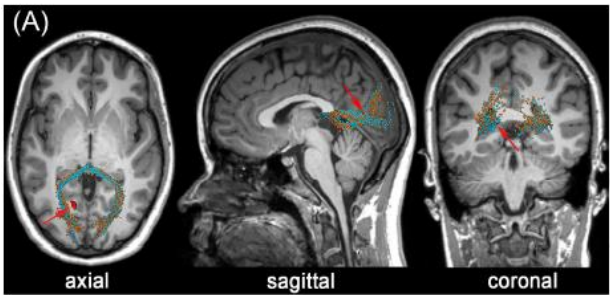

Figure 1A. A representative sample of DTI streamlines passing through the area of a ~ four mm^3 CMB (red) in an old adult host of mTCI. Arrows show a CMB in the left hemisphere, close to a streamlined bundle belonging to the splenium of the corpus callosum. (A) Standard views (coronal, sagittal, axial) of *T1*-weighted MRI were shown in addition to DTI glyphs related with perilesional WM streamline bundles imaged acutely (orange) and nearly six months after injury (light blue). The splenium is unusually asymmetric at both time points, with the asymmetry being most noticeable close to the CMB (inset).

Though CMBs themselves are focal, the study indicates that diapedesis effects can spread far outside the penumbra of the microhemorrhage itself, i.e. outside the immediate CMB zone. Recent studies also suggest that penumbral radii are more widespread in elderly hosts, which may reflect the higher probability of BBB breakage upsurges the severity of TCI sequelae in this patient group. Though penumbral microvasculature may obtain damage during impact which is insufficient to rupture the BBB, following molecular response mechanisms can maladaptively cause the subsequent structural flop of these predominantly vulnerable capillaries. Such a phenomenon may lead to the late development of petechial haemorrhages, which can combine to form iron deposits and then lead to severe problems, including hemorrhagic evolution. The iron deposits moulded after BBB rupture characteristically results from the phagocytosis of erythrocytes, whereby hemi iron in ferritin (i.e., iron bound to hemi co-factors within assured proteins, as well as haemoglobin) was tarnished and dumped in the mode of hemosiderin. As part of the exogenous seditious response to a wound, neutrophils may phagocytise and by this means clear cellular wreckage but may also discharge free militants which injure other parenchymal cells and so proliferate tissue damage.[4,8,9]

Underlying sequelae and procedures of worsening

A recent study showed that, during senescence, microbleeds limited to the cerebral parenchyma are related with the focal permeability of the BBB and with the potentially dramatic reformation of neuronal connectivity, even years after injury. Because blood vessels are usually more flexible than axons, CMB occurrence was proposed to be related with TAI, even though the previous has not been established clearly as a prime indication of the latter. Firstly, higher axonal elasticities do not transform into lesser thresholds for their cut off and splitting as a result of speeding up and slowing forces to which the cerebrum was subjected to substantial influence. Secondly, it is probable that CMB-associated WM injury and necrosis may be the effect of secondary ischemia rather than the effect of the prime axonal injury. With age both the mechanical rigorousness and the threshold for capillary rupture upsurges. However, the frequency of CMB incidence after TCI is prone to increase during senescence and may furthermore relate with TAI far more often than in adolescence. Histological examination remains the method of choice for verifying the biology of WM reactions connected with CMBs. Initial laboratory results from one of the study suggested that, even in mild TCI, CMBs can be related to substantial macro-scale WM alterations in elder patients which may not resolve with time **(Figure 1A).** A vital feature of TCI-mediated CMBs is that they regularly occur at the periphery between cortical GM and WM. This is moderately due to the differences in venous drainage at the GM/WM boundary and due to the distinct mechanical reactions of these two tissue types as they were subjected to substantial physical forces. Because the GM/WM interface is occasionally superficial (superior frontal gyri, middle temporal gyri, etc.) or, other times, deep (insulae,

cingulate etc.) kin to the scalp, one repercussion of both TCI biomechanics and human neuroanatomy is that the spatial circulation of CMBs all over the cerebrum. It can be prevalent and hard to predict across patients. Due to the massive number of long-range, intra-hemispheric WM connections (e.g. corticospinal tract, corona radiata), CMBs can be related with highly-widespread TAI even in mTBI patients, and their number and size can be more significant in older hosts compared to younger hosts for reasons earlier debated.[8,10,11]

It was consistently recognized that older age at the time of TCI is frequently associated with reduced capability for retrieval from CMBs. It seems that older patients relatively poor capability to improve from injuries to the microvasculature was strongly modulated by their commonly deficient endocrine reactions and by their broader neuroinflammatory responses compared to younger patients. For example, a variety of hormones, including insulin, somatotropin, insulin-like growth factor (IGF), thyroid hormone, and estrogens were downregulated physiological responses by proinflammatory cytokines. On the one side, the reduction of these and other neuroendocrine progressions which occur with elderly has a significant effect upon the reduced capability of the cerebrum to recover from TCI. On the other side, whereas microglia plays an important role in neuroinflammation, their mechanisms of action are significantly affected by ageing in many ways, which contain the change of both microglial morphology and of phagocytic activity. Together, these prodigies lead to more substantial oxidative stress and to increased cytokine formation. Somewhat for such reasons, older adults host with acute TCI have multiple cytokine levels and more phagocytosis lacking microglia than younger adults' hosts. Prior study in older TCI victims describes the down-regulation of several genes involved in B-lymphocyte and CD4+ T-cell activity after CMB occurrence–compared to the up-regulation of such genes in younger patients. This may partly describe why both B-cell and immunoglobulin counts were lesser in older TCI survivors than in younger ones. Additionally, during the severe stage of TCI, inflammatory regulatory genes such as leucine zipper transcription factor 2 (BACH2), leucine-rich repeat neuronal 3 (LRRN3) and lymphoid enhancer binding factor 1 (LEF1) were stated at higher levels in younger TCI patients. By contrast medium, older TCI hosts show increased transcriptional activity associated with S100 family genes, including S100 calcium-binding proteins P (S100P) and A8 (S100A8). These two genes are expressed in stimulated macrophages and microglia. It was connected to reduced retrieval from TCI due to the increased inflammatory response regulated by these cell types. Older adults also display reduced activity of members from the altering growth factor β family, which were linked to neural retrieval and rejuvenation. These gene demonstration differences between younger & older adults hosts reflect the higher frequency of positive clinical findings on the chronic cerebral imaging scans of older TCI survivors and recommend a direct association between immune regulation and cerebral retrieval as a purpose of age at injury.[9,12-14]

A vital and under-appreciated feature of TCI in ageing adult hosts is the fact that cerebral responses to it can widen-up over years and years. For example, human neuroimaging scans were confirmed that (A) TCI activated microglia may endure in the cerebrum for as long as two decades after injury. (B) Cerebral inflammation can last for many years, with numerous deadly effects on cerebral function. Moreover, (C) new microvascular anomalies can seem on an everyday basis even long after the injury. Together, these facts appear to describe a complex and poorly-understood cascade of cellular events which provide delayed neural repair despite potentially misleading forms which may recommend that some patients were sufficiently improved.[12,15]

Neuroradiological identification

In clinical settings, a mutual technique to CMB discovery includes the use of SWI and MRI which is highly sensitive to iron buildup in the body. SWI uses a fully flow-compensated, gradient-recalled echo (GRE) pulse sequence which exploits magnetic vulnerability variances between tissues to create enhanced contrast magnitude MRI (images of venous blood, haemorrhages and iron-storing systems). In SWI, CMBs can be described as ovoid, hypo-intense, neuroanatomic foci which are unreliable with osseous, vascular or MRI associated relics. MRI methods such as magnetic field correlation (MFC) imaging, quantitative susceptibility mapping (QSM) and field-dependent relaxation rate increase (FDRI) imaging can also measure diffuse non-heme iron accumulation throughout the parenchyma *in vivo* and hence used to add-on SWI providing info on CMBs. In clinical settings, more and more critical approach for recognising CMB associated TAI includes diffusion MRI techniques such as diffusion-weighted, diffusion tensor and diffusion spectrum imaging (DWI, DTI and DSI). These approaches can analyse the preferred way of water diffusion throughout the cerebrum and in that way detect the sites of physical insults to WM networks. Mapping TAI connected with CMBs can provide clinical and scientific insight above and beyond the capability of further conventional modalities to do so. For example, computed tomography (CT) and conventional MRI [together with *T1*-, *T2*- and *T2**-weighted MRI and even GRE or fluid-attenuated inversion recovery (FLAIR)] can usually isolate relatively large - intra-parenchymal haemorrhages. These methods, yet, do not allow either short- or long-term variations in WM connectivity to be evaluated with quantitative precision, whereas diffusion MRI can significantly assist in this mission.[12,16,17]

A vital task associated with the detection of TCI-mediated CMBs in older adults is that a significant subset of the ageing populace may have CAA linked

CMBs before the injury. For example, CMBs are present in 7% of randomly selected, asymptomatic individuals over the age of 60 who do not have a history of neuropsychiatric illness. Though the simultaneous presence of both TCI and CAA-related CMBs may confound study efforts meant at quantifying injury associated CMBs, some dissimilarities exist between these two forms of pathology. For example, CAA associated CMBs arise more often in profound and infratentorial areas if due to hypertensive arteriopathy or in posterior cerebral areas (occipital lobe) if due to vascular beta-amyloid accumulations. Extra zones usually affected by CAA associated CMBs consist of the mid-subcortical cerebrum and the zones superior to the corpus callosum. On the other hand, TCI mediated CMBs happen more often at the boundary between GM and WM in the cerebral regions where prime injuries are situated or in midline areas, predominantly above the corpus callosum or in medial subcortex regions.[16,18,19]

Clinical significance

The clinical allegations of CMBs in older hosts are debatable. Generally speaking, available scientific and clinical information recommends that post-traumatic CMBs have a substantial adverse impact on the ageing CVS and that the leniency of their impact upsurges with patient's age at injury. Specifically, in older hosts with mTCI, the higher permeability of the BBB, the reduction of neuroendocrine processes (e.g. those responsible for discharging somatostatin and IGF). Moreover, the maladaptive neural repair responses of the developing cerebrum to injury are likely to subsidise substantially to this population's lesser trajectory of retrieval compared to that observed in younger hosts. Though, neuroradiological inspections of mTCI hosts identify CMBs relatively frequently even years after the injury which can ease the task of nursing the temporal dynamics of these events. The long-term results of CMBs remain somewhat unclear. The relationship between CMB presence and clinical outcome in mTCI patients remains predominantly controversial whereas the specific ways in which this type of haemorrhage differentially affects the ageing cerebrum persist incompetently discovered. Some reports suggested a co-relation between CMB presence and TCI associated deficits whereas others had uncertain concerning about the clinical relevance of small hemorrhagic injury. Some insight into this stuff may be achieved from pediatric TCI research. Specifically, CMBs which arise in characteristically developing kids after TCI are statistically linked with neural and cognitive deficits, and this proposes that the functional effects of CMBs in older patients may be like those in kids (however, possibly more noticeable due to ageing processes).[20,21]

In the ageing cerebrum, where the cerebral microvasculature is progressively sensitive to mechanical stress, CMB incidence after TCI is more significant than in younger hosts. In patients with moderate to severe TCI, the adverse effects of remote CMBs upon clinical result may not primarily seem to be nearly as dramatic as those of higher hemorrhagic and non-hemorrhagic lesions. This intuitive reason, nevertheless appealing, does not account for the complex and possibly substantial changes caused by CMB-related TAI upon cerebral regions located far from prime injury spots. Given that such dynamic changes can substantially distress both cognitive and neural function. More study is needed to know the connection between the presence of CMBs in the TCI cerebrum and long-term effects upon high-order cerebral functions. In older hosts with mTCI, the relations between CMBs, histopathology and clinical outcome are predominantly hard to quantify and predict, especially in individuals with contrary, clinical verdicts on *T1*- and *T2*-weighted MRI. One reason for this difficulty is that postmortem neuropathologic investigations were rarely available from mTCI patients who die for other reasons. In the very few such cases which were informed, histopathological investigations were revealed the presence of hemosiderin-laden macrophages in perivascular GM and WM, recommending that axonal shearing is the primary mechanism of mTCI-related cerebral injury. In mTCI hosts with CMBs, substantial co-relations were identified between the number of WM fasciculi injured by TAI and the magnitudes of delays in cognitive response times, which appear to increase with ageing. It appears, thus, that further study required to assess the prognostic value of CMB quantitation relative to that of DTI-based connectivity examination and to disentangle the potential clinical utility of these two methods as a function of patients' age at the damage.[22,23]

Some claim that there is no definite way to conclude CMB chronicity in TCI hosts. However, development in this direction could be made by using neuroimaging to monitor populations at high risk for TCI (e.g. athletes). Firstly, this could afford evaluation of their baseline scans to their post mTCI - MRI interpretations and thereby differentiate recently attained from older CMBs. Secondly, because TCI-mediated CMBs may not be eagerly distinguishable from micro haemorrhages related with CAA, factorial design studies (factors: CAA, TBI) may be valuable for understanding the associative affiliation and interaction between these two pathology types, as well as the supposed differences in their effects upon neural function. We suggest that, barring severe neurovascular or neurodegenerative pathology, TCI mediated CMBs can be similar. If not more common in older TCI hosts than those linked with CAA. Authorization of this suggestion would advise that renewed efforts should be devoted to understanding CMB effects upon the TCI affected cerebrum, instead of in the context of analyses where TCI hosts and TCI free assistants can be stratified, based on their risk factors for CAA. This approach could allow investigators to control for the confusing effects of such risk factors when measuring variances in CMB count, spatial distribution and prevalence between the two populaces. Prominently, the level to which cognitive reserve modulates post-

traumatic neurodegeneration and retrieval, whether in the presence or absence of CAA has not been explored adequately, and upcoming examination should lodge and inspect this significant neuropsychological measure.[20,24,25]

Affiliation to neurodegeneration

The microvascular injury is related to neurodegeneration. For example, the cerebral ageing of adults with a history of recurring TCIs displays hemosiderin deposits and buildups of tau protein in the direct vicinity of blood vessels. Such patients were found to encounter quicker demyelination, the extensive buildup of tau-positive neurofibrillary tangles (NFTs), non-heme iron buildup as well as widespread vascular injury. In numerous TCI hosts, the extent and spatial decoration of these phenomena are often suggestive of those noticed in TCI free folks affected by intellectual impairment. Amyloid sediments were also usually found within micro hemorrhagic foci in mouse models and human familial Alzheimer disease. TCI mediated CMBs are visibly different from those due to CAA or to other neurodegenerative illnesses if only based on the standard of their causative issues. However, the effects of these two CMB types upon cerebral function may share mutual topographies beyond those associated with the mechanisms of their incidence and may as well associate their effects upon cerebral function. In this manner, the extent to which TCI mediated CMBs can subsidise or even worsen CAA and neurodegeneration, in general, was not quantified sufficiently. To this end, future revisions should compare mTCI survivors to TCI free control helpers while classifying all contestants based on their CAA associated ecological risk factors. This tactic could deliver valuable visions into the differential effects of CAA *Vs* TCI mediated CMBs upon attention, executive control and memory, all of which are regularly wedged in both TCI and CAA related neurodegeneration and cognitive degradation, though potentially in different ways. It is reasonable to theorise that information of cognitive reserve at the time of damage can support in defining the likelihood that SWI-detectable CMBs are related to either CAA or TCI. If this is the case, this essential neuropsychological measure could allow scholars to inspect the association between CAA and older adults' susceptibility to CMBs after TCI.[26-28]

Apolipoprotein E (apoE) polymorphisms control many neuroinflammatory responses and to speed up neurodegenerative pathology after TCI. These factors may control CMB progression as well; in animal replicas, DTI trials of WM injury was linked to physical abuses effected upon axons stained with amyloid predecessor protein, to loss of myelination, to increased penetrability of neuronal membranes and to other forms of pathology which are usually detected in neuro-degenerative illnesses. As in such circumstances, the survivors of frequent TCI exhibition substantial, redox-active non-hemi iron accumulation in the hippocampus and within the inferior temporal cortex. These hosts frequently also feature chronic upregulation of hemi-oxygenase 1 (HO-1), an enzyme which worsens hemi-bound iron into free iron and which subsidises to iron excess. hemi-oxygenase 1 is well known as a macromolecule involved in the pathologies of numerous neurodegenerative illnesses of ageing, where its upregulation endorses astrocytic iron buildup, oxidative stress and mitochondrial iron impounding. Older adult hosts are having unique structural and functional variations prompted by mTCI-mediated CMBs. Nevertheless, may specify that personalised therapeutic tactics are likely essential for their healing. To get a complete understanding of how micro-haemorrhages can cause or intensify secondary cerebral damage in older adult hosts, future researchers should examine the mechanisms whereby hemi-oxygenase 1 facilitates such phenomena as a function of age. Additionally, because of neural responses to mTCI may continue for decades after injury and subsidise to patients' vulnerability to neurodegenerative illnesses such as Alzheimers and Parkinsons disease. Understanding why and how the cerebral ages faster after mTCI should be highlighted as a vital study object.[26,29,30]

Conclusions

The narrative on the topic revised here recommends many vital instructions for future investigation. Firstly, more basic science research should try to improve CMB sequelae in animal models of the TCI affected, ageing cerebrum. We detected some foremost exact goals in this esteem, they are

- Endorsing curative revascularisation.
- Reducing cytokine levels in CMB affected areas.
- Interrupting the degradation of hemi-bound iron.
- Improving oxidative stress at BBB rupture places.
- Stimulating macrophages phagocytic aptitude.
- Increasing immunoglobulin manufacture.
- Slowing NFT accumulation in the CMB (pen)umbra.
- Stimulating the re-myelination of TAI affected axons in the CMB (pen)umbra.

Older adult hosts' comparatively high susceptibility to TCI-mediated CMBs specifies that next generation healing interventions should be personalized to the specific requirements of this, particularly susceptible populace. Such interventions should aim to cut down ageing associated deficits in the cerebral systemic response to damage and to lodge the potentially severe consequences of CMBs. Historically, no clinical test assessing neuroprotective mixtures for the healing of TCI has been successful partially because the clinical effectiveness of many such mixtures hinges on their management before rather than afterwards TCI. However, the study aimed at reversing microvascular injury in the ageing cerebrum was recognised compounds which can endorse therapeutic revascularisation even if give out after TCI. One such mixture is fucoidan, a fucose based sulfated polysaccharide which can reduce neuronal apoptosis, lipid peroxidation, reactive oxygen species (ROS) generation and mitochondrial dysfunction. These

observed benefic effects which are probably mediated by the stimulation of Sirt3, a deacetylase from the sirtuin class of proteins which is localized within the mitochondrion and which is well known for its participation in ageing processes. Fucoidan treated elder rats displayed substantial drops in lesion volumes as well as enhancements in sensorimotor function, in spatial learning and memory development. Given the scarcity of presently available lifestyle interventions which can precisely target hemorrhagic lesions in TCI hosts, the efficacy of this and other compounds with similar beneficial effects should be studied in detail.[31-33]

From a neuroimaging lookout, the ability to differentiate between CAA and TCI mediated CMBs using currently existing MRI sequences remains a substantial goal and challenge. The differences between these two types of haemorrhages should be examined more actively to realise (A) the differential effects of these two CMB types upon the ageing cerebrum. (B) the way in which cognitive reserve modifies retrieval. (C) Their potential interface in modulating clinical outcome. Forthcoming MRI systems for imaging the TCI affected cerebrum in the acute stage of injury could exploit variances in structural neuropathology between 'older' (CAA mediated) and 'newer' (TCI mediated) CMBs to differentiate between the two. Such an aptitude could significantly enhance our capability to study how fundamental CAA can modulate cerebral responses to TCI, and may even lead to a finer understanding of CAA itself. Lastly, it is vital to highlight that upcoming studies should especially target older TCI hosts above and beyond the possibility of other enduring efforts in the field of basic, translational and clinical cerebral injury investigation. The elderly signify a prominent and growing demographic section of the populace affected by TCI such that upcoming interventions which take into account the distinct requirements of older TCI survivors should be combined into geriatric care procedures. This could synergistically modify TCI courses in older sufferers, with hypothetically substantial effects upon hosts welfare and quality of lifespan.[32,34,35]

Declaration of Conflicting Interests

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