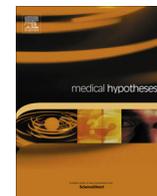


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Stroke, mTBI, infection, antibiotics and beta blockade: Connecting the dots[☆]

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ABSTRACT

Several themes supported by a robust literature are addressed in this clinical translational review and research paper: (1) the inadequate standard of care for minimal traumatic brain injury (mTBI)/concussion when compared to stroke because diagnosis and care for mTBI/concussion are based primarily on a symptom only framework; (2) the treatment of stroke (brain injury) infection with select antibiotics; (3) the use of beta blockade in stroke (brain injury).

The various etiologies of brain injury appear to coalesce to common endpoints: potential neuronal demise, cognitive and functional losses, immune suppression and infection. The use of principles patterned after 'Koch's Postulates' (show/prove the presence of infection/illness/disease, treat until resolved, and prove objectively that the disease/illness is gone/healed/cured) appears to be marginalized in establishing a diagnosis and recovery from mTBI/TBI. The pathways of immune system interactions in stroke (brain injury) and infection are briefly discussed. The suggestion of combined specific antibiotic and beta blockade for ischemic stroke (brain injury) and mTBI is advanced for treatment and expeditious further study. Stroke is considered a brain injury in this paper. Stroke is also considered and recommended as a study model for mTBI therapy because of their common end points from brain damage. It is suggested that potential transfer or translation of therapy for stroke may be useful in mTBI.

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Introduction

Ischemic or hemorrhagic stroke and other brain injury are among the most devastating events patients may suffer. The morbidity and mortality of ischemic stroke and mTBI/TBI remains high. In addition to devastating physical losses, metabolic effects, and immune system deficits, the patient may also sustain long-term psychological damage which can exacerbate other co-morbid injuries. A part of the brain is injured, may die, and with that so do functions the brain and patient once easily accomplished.

In the author's view, a stroke is a brain injury, it is traumatic, and its symptoms may mimic other head traumas. The brain injuries that seem to result in the same endpoint despite having differing etiologies include stroke, mTBI/concussions, blast traumatic brain injury (blast TBI), and any sport/athletic concussions. Motor vehicle or bike accidents, and open traumatic brain injuries are among other frequent causes. These injuries have

differing etiologies but appear to coalesce around immune suppression, brain/neuron damage, infection, inflammation, cognitive or physical deficits all of which may express potential similar molecular pathways.

As with strokes, the various brain injuries can damage the brain tissue organically. Research is just beginning to compare chronic and repetitive athletic injuries to studies of brain injuries from blast trauma TBI [1,2].

The standard of care issue

Soldiers and athletes sustain concussions frequently. This may be from combat, actions and training similar to combat, and during athletic and sports events and training activities. The National Football League (NFL) has adopted newer and 'better' concussion evaluation methods, but they still inappropriately base most of their decisions about athletes' brain injuries predominantly on symptoms. Most other sports with high mTBI/concussion potential are no different. Our young/children athletes suffer the same brain injuries as do our soldiers, adults or professional athletes, with equal ignorance or denial of appropriate evaluation or care. There are not enough studies that compare actual brain healing with psychological symptoms or deficits, but evidence is accumulating

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and deserves more clinical attention and use. A comparative evaluation of the corpus callosum with diffusion tensor imaging (DTI) in acute mild and moderate traumatic brain injury found brain damage in human patients with continuing symptoms that correlated with psychological testing at 6 months from injury with no difference in mTBI/concussion and moderate TBI [3]. Greenwald et al. found that despite the absence of symptoms and negative patient self-reports that thorough psychological evaluation showed the presence of cognitive deficits, demonstrating the importance of this evaluation tool in establishing the presence or absence of symptoms [4].

Earlier studies of brain injuries in acute and chronic settings by Lipton and Kraus established a relationship of acute and chronic mTBI/concussion with objective proof of brain injury and symptoms [5,6]. Lipton's studies at the moment of acute injury/concussion using DTI revealed axonal brain injury which correlated with cognitive losses and deficits in executive decision-making. Kraus used DTI to study human mTBI/concussion injured patients with ongoing cognitive losses and symptoms 6 months after injury and correlated persistent brain damage with these cognitive losses and symptoms. Diffusion tensor imaging (DTI) is a step in the sequence of doing an MRI (Magnetic Resonance Imaging). The radiologist enters the MRI scan sequence, and it is accomplished. The cost is not high, and is a likely part of normal MRI procedural cost. Kraus and Lipton's early objective radiological brain injury studies produced points on the timeline of brain injury that could be used to follow and show brain healing or failure to heal in serial fashion [5,6]. Serial scan assessment is performed routinely in stroke cases, but not in cases of mTBI/concussion. Lipton's and Kraus' brain injury studies are consistent with principles patterned after routine medical practice such as 'Koch like Postulates' for infection, which may easily be brought into the 21st Century and 'translated' for evaluating mTBI/concussion.

Koch's Postulates are named after Robert Koch, the 19th Century microbiologist who refined the notion to prove bacteria were a cause of infection, and after treatment proved that the source of the infection was gone and the patient was free of disease. More explicitly stated, Koch's four Postulates are:

- (1) The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms. (21st century interpretation may be that "prove presence of mTBI/organic brain damage by initial psychological tests, AND objective radiological tests/scans) AND then prove absence of disease/mTBI in asymptomatic patients by psychological tests AND objective radiological tests/scans AFTER apparent health goals reached." Serial exams of both types of tests to follow progress or absence of healing progression may be useful to guide therapy or needed changes.
- (2) The microorganism must be isolated from a diseased organism and grown in pure culture. (21st century interpretation may also be derived from/by objective radiological/scanning information after symptoms are resolved, but illness/brain injury still potentially present.)
- (3) The cultured microorganism should cause disease when introduced into a healthy organism. (Practical 21st century application to brain injury/concussion could be other patients with the same brain injury needing serial proof of healing before and after symptom resolution.)
- (4) The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent. (21st century interpretation may be comparing original psychological testing

AND objective radiological tests/scans to end of care test results to assure complete brain healing, not simply absence of symptoms.)

These principles may be applied in an interpreted and translated form to say simply:

- (1) Objectively prove presence of symptom and damage/injury to the concussed brain by BOTH psychological testing and radiological scans.
- (2) Objectively prove absence of symptoms AND damage/injury to the brain with BOTH psychological testing AND objective radiological testing/scans after treatment goals are reached.

This rigorous assessment of therapy or similar studies and procedures are as highly desirable as the standard of care for mTBI/concussion as it is in stroke. 'Koch's Postulates' are used only as an example of a method of guidelines to prove presence, ongoing treatment and absence or healing of illness after a course of treatment, not only causality. This thorough method appears to be absent in evaluation and treatment of mTBI/concussion. DTI may become a standard evaluative tool, but despite many positive literature reports has not yet emerged as a commonly used method. It is what we have now, and deserves more use and trials. Medical costs can be determinant in providing medical care, but in this case it does not appear to be so. Other recent and potentially useful specialized radiological studies in evaluating brain injury are Magnetic Resonance Imaging Spectroscopy and Gradient Echo (GRE), and High Definition Fiber Tracking, for example.

In medicine, there are cases in which the disease or injury remains after symptom resolution. This is the case in stroke and mTBI. Therapy may need to be continued in the absence of symptoms. We must seek objective proof for absence of damaged brain tissue in mTBI (axonal, white matter, etc.) and show that the patient is not only symptom free but also injury free. DTI or others could become a procedure to show this with until a better one is available. This may be desirable as the practiced standard of medical care. Compared to stroke, mTBI/concussion has become an injury in which primarily symptoms only are sought and treated.

A psychological questionnaire may show the presence or absence of symptoms. It is also clear that there are patients who have a brain injury without symptoms and lengthier cognitive examination may make symptoms 'visible' [4]. Brain injuries/mTBI/concussion can be undiagnosed, under-diagnosed, untreated or simply ignored, leaving the patient in danger. Perhaps it is timely for neurologists, neurosurgeons and radiologists to weigh in on developing and adopting a more objective endpoint of care for concussed patients? The literature on use of DTI as a 'beginning' scan is robust, and promises to lead to more sophisticated scanning studies and methods.

The military symptomatic blast exposed or mTBI/concussion patient is evaluated and re-evaluated by various computerized cognitive and behavioral assessment tools. These are a valuable starting tool to show that symptoms are present or not. If symptoms are present, then there is organic brain damage. Psychological tools must be combined with radiological studies that show definitively presence, absence or healing of brain injury. If soldiers who may continue to have brain damage but are asymptomatic are re-deployed or returned to duty (RTD) without scientific evidence of true brain injury healing, re-injury or new injury in the same or another part of the brain may potentially result in devastating and chronic damage. Medical decisions in brain injury/mTBI should be based on scientific evidence, dictated by using principles based on 'Koch like' Postulates as a standard of care. In most cases, athletes who have sustained concussion return to athletic competition when their symptoms are gone, and

evidence of healing is not the basis of an objective medical evaluation to return to normal athletic activities. mTBI/concussion is a physical tissue injury to the brain with psychological symptoms and chemical and metabolic imbalances. mTBI/concussion, like stroke, is not a purely psychological symptom and cognitive condition. We may look at the stroke model to teach us about mTBI/concussion therapy, injury visibility and standard of care.

Stroke (brain injury), mTBI, and the immune system

Brain trauma suppresses the immune system and this is well supported in the scientific literature, but often ignored by medical providers. Selective legacy reports chronicle the effects that brain trauma and stroke have on the immune system: decreases in the numbers and functions of several types of T-lymphocytes, Natural Killer (NK) cells, cytokines and receptors, and decreases in neutrophil superoxide release, immunoglobulin G (IgG), immunoglobulin M (IgM), complements C1q and C2, among other factors [7–9]. A shift within the cellular immune system from ‘Th1’ dominance type to ‘Th2’ dominance via the action of catecholamines, corticosteroids and cytokines in brain trauma, stroke and subsequent infection was recently re-examined and potentially connected with bacterial translocation from the gut in trauma and brain trauma. Adoptive immune therapy in cases of nosocomial infection was also considered [10].

An early report by Lennard and Browell suggested a dose response effect by trauma on the immune system. Immune suppression and difficulty of recovery increases as the trauma increases or endures [11]. Recently Weimar noted that initial stroke volume is an independent predictor of outcome, supporting the results of an earlier report [12,11]. Hug et al. studied the relationship between stroke infarct volume, immune cell function, infection susceptibility and noted that infarct volume was a principal factor causing lymphopenia several days after stroke [13]. They supported some of the earlier reports of stroke immune system suppression and that tumor necrosis factor alpha (TNF alpha) reduction by monocytes was associated with infections [7–9]. Stroke volume prevailed as an independent early post-stroke pneumonia and higher mortality predictor.

Recovery to pre-injury health is made more difficult because immune suppression causes problems not usually addressed in the overall care plan. Emsley and Hopkins support that post-stroke immunosuppression is an independent factor for increased infection susceptibility [14]. They correctly hypothesized that the hypothalamo–pituitary–adrenal axis (HPAA) and sympathetic nervous system (SNS) activation may trigger general counter-inflammatory mechanisms (Th2 immune system type) that may further enhance potential for infection.

Emsley described systemic anti-inflammatory changes affecting the brain’s response to stroke and trauma [15]. Inflammation in thirty-six patients with ischemic stroke showed increases in C-reactive protein up to three months after stroke. Interleukin 6 (IL6) was also elevated, predominantly with infection at 30 days post-stroke [15].

Ischemic stroke (brain injury) and infection

Immune suppression, decreases in TNF alpha levels, elevation of IL6, inflammation and stroke size are among the factors that appear as characteristics of post-stroke infections. In a meta-analysis of post-stroke infections, Westendorp et al. reviewed the association between post-stroke infection and outcome in eighty-seven studies involving 137,817 patients; eight studies (~11%) were from patients admitted to an intensive care unit (ICU) [16]. They found an overall infection rate of 30%

(24–36%), and pneumonia plus urinary tract infections (UTI) of 10%. For the ICU patients the infection rates were higher—45% overall, 28% pneumonia and 20% UTI’s. The ICU patients may have had a larger stroke volume or co-morbidities. Stroke (brain trauma) suppressed immune responses, and inflammation also caused a poor tissue regeneration response with depressed wound healing. Chamorro et al. support Emsley et al. that infection after acute ischemic stroke is aided by brain-induced immunosuppression and that the size of the stroke is a strong determinant of infection with higher mortality [17,14].

Grabska et al. studied 1950 patients with ischemic strokes over a ten-year period and found that pre-stroke infections predicted a worse short-term outcome, and that in-hospital (nosocomial) infections predicted poor short and long-term outcome (30 and 90 days) [18]. Patients with pre-stroke infections fared worse than uninfected patients and had a higher pneumonia rate (81%) and mortality. Their rate of nosocomial pneumonia was 19.5%, and that of UTIs were 23.3%. A total of 7.5% of stroke patients developed both pneumonia and a UTI nosocomially. Involvement of at least one brain lobe with stroke predicted a higher nosocomial infection rate.

Dysphagia after stroke was associated with a higher pneumonia rate of 86.6% [18–20]. Pneumonia is an independent risk factor for poor outcome (death). UTI’s had a lower rate of short-term poor outcome. Patients with nosocomial pneumonia and standard antibiotic therapy showed no decrease in mortality [18], and only the UTI population had a 14% decrease in mortality. The pneumonia patients died of complications from infections, not neurological demise or cardiac disease. High temperature was also associated with a large infarct [21]. Fassbender et al. also report a higher incidence of nosocomial infections after stroke with a rate of 27% of 52 patients while Hilker reports a 21% pneumonia rate in 124 patients in a neurological ICU [22,23]. Adding to earlier reports, Chamorro’s excellent review of infection after ischemic stroke also supports that dysphagia and aspiration are predictors of pneumonia, that worsening infection may not affect stroke, and suggests also that both are independent co-existing morbidities [24].

Ischemic stroke (brain injury) and antibiotics

Chamorro’s group randomized 136 human patients in a double blind fashion and treated them with levofloxacin at a dose of 500 mg daily for 3 days within 24 h after stroke onset. The study was stopped because post-stroke infections were not prevented nor was there improved outcome [17]. However, in Harms, Prass and Meisel’s PANTHERIS (Preventive Antibacterial Therapy in Acute Ischemic Stroke) study 78 human patients were given moxifloxacin 400 mg daily for 5 days via IV infusion within 36 h after ischemic stroke to treat pneumonia and UTI [25]. In the study, 42% of placebo treated patients developed infection post-stroke, while only 17% moxifloxacin treated patients developed infection showing a significant decrease in the post-stroke infection rate. Compared to Chamorro’s three day course of levofloxacin, they credit the longer administration of antibiotics with reducing the infection rate. They also suggest as do Chamorro et al. that while aspiration is a major source of post-stroke pneumonia, the more likely reason for the high incidence of infection is immune suppression, combined with post-stroke aspiration. Many patients without stroke or immune suppression aspirate but suffer pneumonia less frequently. Harms et al. show in their human PANTHERIS study neurological outcome and survival were not significantly influenced or enhanced by moxifloxacin in post-stroke treatment [25]. Meisel et al. also used moxifloxacin for ischemic stroke in a mouse model and showed some decrease in stroke volume [26]. As with Harms’ human study, the infection rate was

reduced, but stroke survival and mortality was not improved. Khlemet and Harms et al. confirmed that human stroke patients with infections showed a lower CD4 + cell count and higher urinary levels of norepinephrine than stroke patients without infections [27]. The onset of infection increased the plasma IL6 level but this increase was not observed in the moxifloxacin group. An incidental important finding was that some patients who received moxifloxacin had an infection despite the use of an antibiotic also showed an increase in plasma interleukin 10 (IL10) levels. We may look to the action of catecholamines on IL10 excretion and the role of IFN gamma in the immune response for potential explanation as a critical immune response pathway appearing negatively affected: IL10 reduces IFN gamma production, thus preventing early activation of leukocytes to fight infection as response to the antigen presenting cells [28,29]. Moxifloxacin activity against infection in the remaining 17% still infected could be potentially overcome by blunting the effect of catecholamines on IL10 to decrease IFN gamma causing an ensuing Th1 to Th2 shift which may not address invading bacteria and infections [27] with beta blockade. The patients in the sub-set described above who had increased IL10 and developed infection despite moxifloxacin treatment could comprise the 17% of stroke patients still infected. Prass et al. also offers the plausible explanation of a Th1 to Th2 immune shift as outlined above [29]. Several interactive steps form a complex cascade with antigen presenting cells (APCs): 'Th' helper cells, CD4 + cells, catecholamines, cytokines (IFN gamma, IL2 and IL12, IL 10 and IL6, TNF alpha, for example, and corticosteroids). These moieties form a dynamic and complex interactive series of reactions and paths within the cellular immune system for a specific response to 'allow' immune suppression' and infection. The pathways may be diagrammed as follows (see Fig. 1):

Beta blockade in stroke (brain injury): of mice and men

Evidence regarding the role of beta blockers or agonists in the role of leukocyte populations and responses was noted in 1989 by Maisel et al. who found that the beta receptor agonists terbutaline and isoproterenol showed a differential result in varying T-cell populations in human patients: terbutaline decreased beta

receptor numbers, and isoproterenol stimulated cyclic adenosine monophosphate (c-AMP) [30]. Landmann and Anstead et al. showed the variability of peripheral blood lymphocyte beta-2 adrenergic receptor densities in humans [31,32].

The study by Maisel (1989) is supported with other human studies by Suberville et al. in 1996, and by Schroder et al. [33,34]. Suberville et al. discussed the regulation of IL10 by beta adrenergic agonists [33]. They showed an increase in cyclic AMP with isoproterenol, a beta agonist and a subsequent increase in interleukin 10 (IL10) that decreased TNF alpha synthesis. The increase in IL10 was significantly reduced by oxprenolol, a beta-blocker. This study appears to be the first to demonstrate that a beta antagonist (oxprenolol) reduced serum IL 10. Schroder describes that interferon gamma (IFN gamma) coordinates a diverse array of programs intra-cellularly that act through relevant genes [34]. Macrophage activity is enhanced in responding to infection by up-regulation of pathogen recognition, antigen processing and presentation via APCs, apoptosis, and interaction with TNF alpha. In 1997 Doecke et al. discussed that INF gamma neutralizes the inflammatory cytokines TNF alpha or interleukin 1 (IL1) and decreases mortality of sepsis in human patients [35]. Their small study of monocyte activation with INF gamma resulted in clearing 8 of 9 human patients of sepsis with enhanced survival. Herrera showed that IFN gamma and IL10 cross-regulate and oppose each other in re-programming macrophages [36]. Building upon these legacy studies in beta blocker-cytokine interactions, Prass et al. used a murine model to induce middle cerebral artery occlusive ischemic stroke, suppress the cellular/innate and adaptive immune system, and induce pneumonia and sepsis [29]. They ameliorated the pneumonia with propranolol, a beta-blocker, but not the sepsis. The sepsis was ameliorated with adoptive immune therapy by prior cryogenically stored autologous WBCs. The beta blocker results support the earlier studies by Suberville and Doecke: blocking the effect of catecholamines in reducing IFN gamma production by IL10 and thereby not allowing the T-lymphocytes to attack the infection [33,35]. This mechanism and adoptive immune therapy may also have major implications for a current health problem: hospital acquired or nosocomial infections occurring in situations other than in cases of stroke or brain injury. This potential was addressed

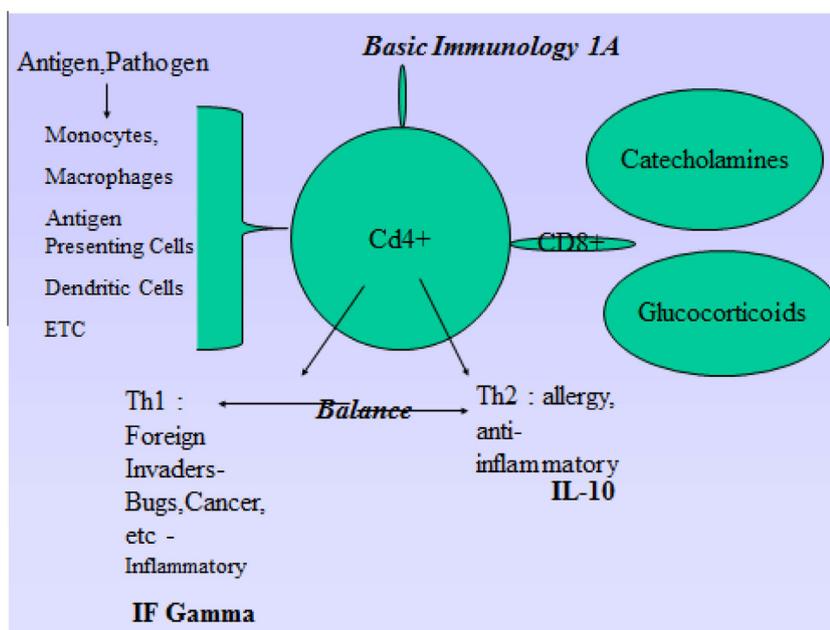


Fig. 1. Antigen presenting cell 'change' the CD4 + cells into Th1 or Th2 cytokine producing cells that affect and re-program T-cells.

and proposed in an earlier paper where increase in bacterial translocation from the gut was suggested as a possible source of infection because of brain trauma induced immune suppression [10]. The 2003 murine study by Prass et al. fulfilled the principles based on 'Koch like' Principles to find clinical utility for adoptive immune therapy in ameliorating stroke induced sepsis after treatment with a beta-blocker for the pneumonia [29].

A large study by Dziedzic et al. in 2006 addressed using beta blockade in human ischemic stroke patients [37]. Dziedzic's group studied 833 ischemic stroke patients, 88 (10.6%) of whom were on and continued to receive beta blockade while hospitalized for ischemic stroke. They concluded that the adrenergic or catecholamine activation attenuation by beta blockade was beneficial, that it drastically reduced mortality after ischemic stroke by preventing immuno-deficiency and reducing pneumonia from 11.4% in the pre-stroke population to 4.5%. Dziedzic noted that most of these patients were already on beta blockers and had an overall lower stroke and cardiac mortality. Of note is an already lower infection rate on the pre-stroke beta blocked population than the usually quoted higher figures. Beta blockade also showed neuro-protective properties with anti-oxidant and anti-inflammatory effects. The major finding of this study is the startlingly low beginning incidence of infection in beta blocked stroke patients of 11.4%. The fact that beta blocker use prior to and after ischemic stroke reduced the pneumonia rate to a 4.5% overall infection rate by continued beta blocker use absolutely overshadows minor study limitations and allows the conclusion that beta blockers may be useful in drastically reducing infections in stroke, potentially in mTBI, and in nosocomial/hospital acquired infections. A strongly needed and advocated strategy by the author is trials of combined moxifloxacin/levaquin and beta blocker therapy in infected ischemic stroke, mTBI/concussion and nosocomially/HAI infected patients.

Traumatic brain injury of different etiologies including mTBI/concussion in war injured veterans shows occurrence of infections at roughly the rate expected in stroke. A respiratory disease rate of 20.44% and a 10.67% UTI infection rate was noted [38]. The bacterial spectrum in sputum and urine included *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, MRSA, *Enterbacter cloacae*, *Streptophomonas maltophilia*, and *Acinetobacter baumannii*. Seventy-one percent (71%) of *K. pneumoniae* and sixty-seven percent (67%) of *Acinetobacter* isolates were resistant to multiple drugs. These bacterial infections were not treated with moxifloxacin or quinolones nor with beta blockade. The bacterial spectrum for Meisel's findings had only *E. coli* as a common infectious agent [26]. Westendorp et al. speak of some of these causative organisms as nosocomial sources of infection in aspiration pneumonia [16]. More comparative studies are indicated. McKee noted that as many as 20% of the ~2.3 million troops deployed overseas may eventually also suffer from Chronic Traumatic Encephalopathy (CTE), with symptoms similar to dementia including cognitive losses and depression [1].

Discussion

The principle that the brain may not be healed even if the symptoms are gone is usually not addressed by current health practitioners, with potentially devastating results in cases of sports head injuries, repetitive head injuries, mTBI/concussion and blast injuries, and other common head injuries. Perhaps it is too early in medicine to go 'out of the box' in immune resuscitation therapy and models. It should not be too early-our stroke and concussed patients deserve better. However, as the above discussion points out, a potential model may be beta blockade early in the injuries, and this seeks serious attention and further study. Infections may be lessened greatly, as well as those acquired nosocomially. The

use of principles based on 'Koch like Postulates' or objective proof of a healed brain would ensure that the standard of care shows objective evidence of brain healing in the absence of symptoms for mTBI and concussion. Using questionnaires and tests seeking psychological symptoms as the only basis for establishing a diagnosis and end of treatment of brain injury may violate this principle. There are rare objective study models available besides radiological exams, but these await further attention and utility. The military use of MACE (The Military Acute Concussion Evaluation) is a brief scoring system enabling the medics and ER personnel to gage cognitive losses [39]. Unfortunately it too is based only on symptoms, but allows removal from combat duty after three consecutive 'concussions' in the same deployment. This may not be sufficient practice, given the fact that a symptom free concussed brain may not be an injury free healed brain. The MACE literature states that its use should be combined with a more thorough radiological evaluation, but this is rarely done. As in athletics, symptoms are the predominant determinant of therapy, not evaluation of organic brain damage by available radiological procedures. The definitive proof that the brain has healed from a trauma/concussion may be offered by DTI or other specialized radiological studies. DTI may also be useful in differentiating symptoms that overlap between mTBI and PTSD, post-concussive syndrome notwithstanding. There may be objections to DTI or other objective radiological procedures by some care givers because of the 'newness' of it, but adding DTI or other diffusion mode is easily implemented and causes little inconvenience. The gains and health of our concussed patients however is immeasurably enhanced. Making a medical decision on less than objective evidence available today may reflect inadequate medical practice. Serial scans are the standard of care for stroke patients but not for mTBI/concussion patients.

Infection, systemic inflammation, infarct size and high body temperature are independent predictors of a poorer stroke outcome. Pre-stroke infections and dysphagia lead to higher infection rates and indicate higher mortality. Immune suppression from the effect of catecholamines on cytokine excretion from stroke or brain injury leads to infections such as pneumonia, UTIs and sepsis. Use of moxifloxacin reduced the infection rate in humans from 42% to 17% if given at a dose of 400 mg daily for at least 5 days after the onset of ischemic stroke. Patients already on beta blockers seem to have a lower rate of infection in stroke than those patients not on beta blockers because cholinergic or adrenergic blockade may allow interferon gamma to maintain a Th1 cellular immune posture to fight infection. Continued treatment with beta blockade reduced the pneumonia rate in ischemic stroke in human patients to 4.5% when continued post-stroke in the ICU/hospital. Ischemic stroke or infection are also independent variables of stroke mortality. Curing the infection will not stop neurological demise, nor will curing the stroke or brain injury stop infectious and septic demise. It is suggested that moxifloxacin or levaquin and beta blockade be used together for ischemic stroke and other brain injury for the best potential patient outcomes, and studies must be performed expeditiously to confirm the efficacy of the combined use of this potential life-saving therapy. Outcome studies seem indicated and are easy to perform, with statistically significant results easily achievable from the large patient populations suffering from stroke and mTBI/TBI.

Conclusion

Ischemic stroke and mTBI/concussion may result in complete, partial or no recovery, with multiple potential co-morbidities. Both lead to brain damage, cognitive and functional losses, immune suppression, and infection. The convergence of stroke and mTBI into like sequelae may suggest focused efforts to find

common therapeutic solutions. Soldiers, first responders, police, all types and ages of athletes may incur multiple head injuries on a daily basis, not just from their 'work', but also in training for these activities. Concussed/mTBI or stroke patients may benefit from studies using beta blocker early in the treatment to help maintain a robust immune response. Infection in ischemic stroke was decreased in beta blocked patients upon suffering stroke. Continued beta blockade after stroke reduced infection while hospitalized [37]. Moxifloxacin used in the acute ischemic stroke also reduced infection rate [25]. Adoptive immune therapy or autologous white cell re-infusion may also be beneficial [10,29].

We can learn much from stroke patients about therapy and evaluation for our concussed soldiers and athletes, including making the mTBI/concussion injuries more visible. The stroke therapy and sequelae model may be transferable to mTBI as an experimental and study example. The supportive framework of the brain is also injured in stroke and mTBI/concussion and can benefit from a healthier immune system to help to heal the damaged brain. 'Koch's Postulate' like based principles, as objective proof of a healed brain and not only absence of symptoms, must be the standard of care for mTBI/concussion as it is in stroke.

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