Review Article

Physiotherapy and Occupational Therapy Journal
Volume 8 Number 4, October - December 2015
DOI : https://dx.doi.org/10.21088/potj.0974.5777.8415.4

Role of Genetic Susceptibility in Second Impact Syndrome: A Focused Review

Harshita Yadav*, Manisha Uttam**

Abstract

Second Impact is a set motion cerebral vascular congestion which results in cerebral swelling. Death usually occurs due to transtentorial brainstem herniation. Due to rapid deterioration following acute injury some genetic markers like apolipoprotein (APOE) is associated with neurogenic responses resulting in low performance in sport related head injury. If the symptoms persists for long duration this may further predispose it to second impact which might be associated with APOE allele carriers as postulated by many authors. Further evaluation for the associated factors between APOE and second impact syndrome (SIS) is needed which helps in understanding genotype linkage with severity of head injury.

Keywords: Repetitive Head Injury; Concussion; Traumatic Brain Injury; Genetic Markers; Cerebral Edema; Cerebral Haematoma.

Introduction

SIS of "Catastrophic head injury", term had been coined by Richard Schneider in 1973, sharing a similar pathophysiology to repeated concussive injury. SIS syndrome typically occurs when an athlete sustaining an initial head injury and then suffering a second head injury before the symptoms associated with the first impact have resolved[1].

Pathophysiology

The pathophysiology behind SIS is the failure of cerebral vascular autoregulatory mechanism which ultimately leads to increased intracranial pressure and further results in herniation of temporal lobe or lobes below tentorium through foramen magnum [1-4]. Typically, time taken after second insult to brainstem failure is three to five minutes [1,4]. Cerebral autoregulation is the "tone" of arteries which helps them to uniformly either dilate or constrict for maintenance of cerebral blood flow. Disturbance or absence of this tone is associated with altered blood pressure which results in either hypotension or hypertension. Thus, failure of pressure autoregulation occurs in a linear fashion predisposing it to increased severity of head injury. It is evident that there is 20-30% of patients with autoregulatory dysfunctions following mild head injury and 80% with severe head injury tends to have autoregulatory dysfunction [5].

Focusing on symptoms of sports related head injury and concussion, headache is the one which persists long after first head injury. It becomes a typical sign after second impact along with other symptoms like labyrinthine dysfunction, visual, motor or sensory changes or mental difficulty which usually comes after first impact along with the headache [1].

Risk Factors

SIS being a rare syndrome as postulated by many authors results in diffuse cerebral swelling and a usually fatal outcome. It is being continuously reported by authors that boxers are first one to be listed in risk category of catastrophic brain injury such as subdural haematoma when compared to other sports [6,7]. Only 2 case reports, one being on 16 year old ice hockey player and other on 17 year old gridiron football player have been evidence found for existence of probable SIS in children. As other authors have argued for different cerebral autoregulation response to minor head injury for

Author Affiliation: *MPT (Orthopedics) **MPT (Neurology), Research Scholar, Department of sport science, Punjabi University, Patiala.

Reprint Request: Harshita Yadav, Street No. 5, Arya Nagar, Ballour Road, Bahadurgarh, Haryana Pin Code - 124507.
E-mail: harshitayadav@mmumullana.org

cerebral swelling when compared children with adolescents[3].

Since, a clear picture of risk factor for post traumatic acute brain swelling has not been understood yet, but through present literature it is found that children and adolescent are at higher risk [8,9]. Also, clinical evidence is found stating SIS cases in young males [3,8]. From medical literature on neurosurgical catastrophic brain injury after minor head injury approximately 30% of the cases were found to be female. Therefore, a true gender difference regarding cerebral response to trauma remains unclear. It is speculated from recent discussion that second impact resulting from repetitive head injury (multiple concussion) may have persistence of diffuse cerebral swelling which is a mechanism of post traumatic head injury. Giza and Hovda concluded that it is difficult to state a true duration of vulnerability to second injury [10].

Genetic Susceptibility

A window for potential role on genetic markers influencing outcome from head injury has shown a limelight, suggesting possible consequences, associated factors through its capacity for re-organization, neuronal regrowth and repair. APOE is a plasma lipoprotein which plays a role in nervous tissue healing. All peripheral APOE is synthesized in liver, whereas APOE is preponderant apolipoprotein within central nervous system, where it is majorly synthesized by Astrocytes. Three major isoforms of APOE refers to as APOE 2, APOE 3 and APOE 4 are products of alleles (ε2, ε3, and ε4) at single gene locus and occurs with frequency of 75, 78% and 15% respectively [12,13].

A link between APOE genotype, head injury and alziemer's disease was first reported by Mayeux et al [14]. Also, Nicoll et al. finding indicates, APOE may increase genetic susceptibility to the effects of head injury [15]. APOE genotype was determined and subsequently correlated with neuropathological findings. It appears that any head injury, sports related single concussion or multiple concussions may trigger the position of β- amyloid especially in those who have APOE ε4 [16]. There are studies, which indicate poor outcome in APOE ε 4 carriers for recovery during rehabilitation after head injury [17].

In clinical genetic literature, APOE ε4 allele is found to be associated with attentional impairments and white matter abnormalities and increased risk of Late – onset sporadic Alzheimer's (LOSA) disease. Adverse functional outcomes acutely early and late after severe but not clearly after mild and moderate head injury and also after hemorrhagic but not after ischemic stroke, cardiac surgery and cardiopulmonary resuscitation and probably subarachnoid hemorrhage [18]. Controversially, Smith et al found a relationship between APOE ε 4 allele and severity of contusion and ischemic brain damage but not with other pathological changes after head injury [18,19]. Different authors concluded that APOE ε4 carriers are less able to avoid secondary damage and repair damage tissue after injury. A study by Crawford et al helps in depicting the impaired performance in memory test using some memory and cognitive measures found that patient with ε 4 allele carriers had worse memory after head injury as well as poorer outcome [16, 20].

Ariza et al postulated that influence of APOE on cognitive function and behaviour six to nine months after severe and moderate head injury [16]. Terrelle et al. reported that carrying the APOE promoter allele was associated with self reported concussion history and greater concussion severity in collegiate athletes [21, 22]. This helps in stating that APOE may also influence various clinical aspects of head injury, concussion, SIS including more marked cerebral oedema, increased hematoma volume, greater incidence of moderate / severe contusion injury and ischemic brain damage which further increases the hospital mortality rate [23-25]. Recent evidences from transgenic closed head injury models also supportitive role of APOE in inflammatory response and neuronal repair mechanism following head injury [26-28].

A study by Kuther et al. reported that older professional players carrying ε4 allele and exhibited lower cognitive performance scores versus their non ε4 carrying counterparts. One study reported that 75% of individuals carrying 3APOE rare allele had a history f concussion in collegiate athletes [3, 29]. From a series of studies it is suggested that ε4 allele may exert not only long term influences manifested phase but also short term effects on head injury by worsening the pathological course of head injury in acute stage [16]. The above discussion, helps in understanding the APOE plays a key role with neurogenic responses to the injury in sports. Giving evidence that APOE carriers are at greater risk when compare to non carriers along with which risk of multiple concussion resulting in second impact increases. Since, there is paucity of researchers examining the association between SIS and APOE genotype, therefore there is need to explore the relationship between the SIS and APOE through some clinical trials.

References

1. Cantu RC, Gean AD. Second-impact syndrome and a small subdural hematoma: an uncommon catastrophic result of repetitive head injury with a characteristic imaging appearance. J Neurotrauma. 2010; 27(9): 1557-64.
2. Weinstein E, Turner M, Kuzma BB, Feuer H. Second impact syndrome in football: new imaging and insights into a rare and devastating condition. J Neurosurg Pediatr. 2013; 11(3): 331-4.
3. McCrory P. Does second impact syndrome exist? Clin J Sport Med. 2001; 11(3): 144-9.
4. Cantu RC. Head injuries in sport. Br J sports Med 1996; 30: 286-296.
5. Wetjen NM, Pichelmann MA, Atkinson JL. Second impact syndrome: concussion and second injury brain complications. J Am Coll Surg. 2010; 211 (4): 553-7.
6. Dacey RG Jr, Alves WM, Rimel RW, Winn HR, Jane JA. Neurosurgical complications after apparently minor head injury. Assessment of risk in a series of 610 patients. J Neurosurg. 1986; 65(2): 203-10.
7. Jordan, Barry D.; Campbell, Edwin A. Acute Injuries among Professional Boxers in New York State: A Two-Year Survey. *Physician and Sportsmedicine.* 1988; 16(1): 87-91.
8. McCrory PR, Berkovic SF. Second impact syndrome. Neurology. 1998; 50(3): 677-83.
9. McCrory P, Davis G, Makdissi M. Second impact syndrome or cerebral swelling after sporting head injury. Curr Sports Med Rep. 2012; 11(1): 21-3.
10. Signoretti S, Lazzarino G, Tavazzi B, Vagnozzi R. The pathophysiology of concussion. PM R. 2011; 3: 359-68.
11. Tierney RT, Mansell JL, Higgins M, McDevitt JK, Toone N, Gaughan JP, Mishra A, Krynetskiy E. Apolipoprotein E genotype and concussion in college athletes. Clin J Sport Med. 2010; 20(6): 464-8.
12. Mahley RW, Innerarity TL, Rall SC Jr, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res. 1984; 25(12): 1277-94.
13. Merched A, Blain H, Visvikis S, Herbeth B, Jeandel C, Siest G. Cerebrospinal fluid apolipoprotein E level is increased in late-onset Alzheimer's disease. J Neurol Sci. 1997; 145(1):33-9.
14. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, Chun M, Tycko B, Shelanski M. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 1995; 45: 555-7.
15. Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. Nat Med. 1995; 1(2): 135-7.
16. Sun XC, Jiang Y. Genetic susceptibility to traumatic brain injury and apolipoprotein E gene. Chin J Traumatol. 2008; 11(4): 247-52.
17. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. Lancet. 1997; 350(9084): 1069-71.
18. Houlden H, Greenwood R. Apolipoprotein E4 and traumatic brain injury. J Neurol Neurosurg Psychiatry 2006; 77: 1106.
19. Smith C, Graham DI, Murray LS, Stewart J, Nicoll JA. Association of APOE e4 and cerebrovascular pathology in traumatic brain injury. J Neurol Neurosurg Psychiatry. 2006 Mar; 77(3): 363-6.
20. Crawford FC, Vanderploeg RD, Freeman MJ, Singh S, Waisman M, Michaels L, Abdullah L, Warden D, Lipsky R, Salazar A, Mullan M. APOE genotype influences acquisition and recall following traumatic brain injury. J Neurology. 2002; 58(7): 1115-8.
21. Jennifer M Hootman, Randall Dick, and Julie Agel. Epidemiology of Collegiate Injuries for 15 Sports: Summary and Recommendations for Injury Prevention Initiatives. J Athl Train. 2007 Apr-Jun; 42(2): 311–319.
22. Tierney RT, Mansell JL, Higgins M, McDevitt JK, Toone N, Gaughan JP, Mishra A, Krynetskiy E. Apolipoprotein E genotype and concussion in college athletes. Clin J Sport Med. 2010; 20(6): 464-8.
23. Lynch JR, Pineda JA, Morgan D, Zhang L, Warner DS, Benveniste H, Laskowitz DT. Apolipoprotein E affects the central nervous system response to injury and the development of cerebral edema. Ann Neurol. 2002; 51(1): 113-7.
24. Liaquat I, Dunn LT, Nicoll JA, Teasdale GM, Norrie JD. Effect of apolipoprotein E genotype on hematoma volume after trauma. J Neurosurg. 2002; 96(1): 90-6.
25. McCarron MO, Weir CJ, Muir KW, Hoffmann KL, Graffagnino C, Nicoll JA, Lees KR, Alberts MJ. Effect of apolipoprotein E genotype on in-hospital mortality following intracerebral haemorrhage. Acta Neurol Scand. 2003 Feb; 107(2): 106-9.
26. Lynch JR, Pineda JA, Morgan D, Zhang L, Warner DS, Benveniste H, Laskowitz DT. Apolipoprotein E affects the central nervous system response to injury and the development of cerebral edema. Ann Neurol. 2002; 51(1): 113-7.
27. Chen Y, Lomnitski L, Michaelson DM, Shohami E. Motor and cognitive deficits in apolipoprotein E-deficient mice after closed head injury. Neuroscience. 1997; 80(4): 1255-62.
28. N Nathoo, R Chetty, J R van Dellen, G H Barnett. Genetic vulnerability following traumatic brain injury: the role of apolipoprotein E. Mol Pathol. 2003; 56(3): 132–6.
29. Kimelberg HK. Current concepts of brain edema. Review of laboratory investigations. J Neurosurg. 1995; 83(6): 1051-9.