World Journal of Surgery and Surgical Research

Research Article
Published: 16 Apr, 2019

Immunological Changes Observed in ICH

Rajendra Shrestha[1,3], Reeka Pradhan[2] and Chao You[3]*

[1]*Department of Neurosurgery, NAMS, Bir Hospital, Nepal*

[2]*Paropkar Maternity and Women's Hospital, Nepal*

[3]*Department of Neurosurgery, West China Hospital, Sichuan University, China*

Abstract

Objective: Intracerebral Hemorrhage (ICH) is a one of the stroke subtype with high morbidity and mortality.

Aim: The aim of this prospective study was to assess immunological changes and their clinical significance in patients with ICH.

Method: Sixty patients with spontaneous ICH were evaluated regarding immunological changes by measuring peripheral blood lymphocytes subsets CD3+, CD4+, CD8+, CD4+/CD8+, white blood cell count, lymphocytes count and immunoglobin IgA, IgG, IgM, IgE and IgD level. The relationships of immunological to clinical and radiological parameters were evaluated at hospital admission (t0), 5 days (t1), and 10 days (t2). The results were statistically analyzed.

Result: Immunological parameters were significantly changes with severity of diseases. There were significant changes were observed for leucocyte count, lymphocytes sublets CD4, CD8, and CD4/CD8 at hospital admission (t0), 5 days (t1), and 10 days (t2) in both operative and conservative patients. But there was not statistically significant in immunoglobin level. There were significant positive correlations between leukocyte with GCS (r=0.29, 0.30), Volume (r=0.55, 0.37) and mRS (r = -0.30, -0.47) during admission and discharge time respectively ($p<0.05$). But Leukocyte was negative correlation with CD4 at hospital admission (r = -0.80, -0.33) and discharge (r = -0.37, -0.45).There were negative correlations between CD 4 with GCS (r = -0.28, -0.34), volume of hematoma (r = -0.32, -0.56), mRS (r = -0.38, -0.46) during admission and discharge time ($p<0.05$).

Conclusion: Immunological parameters changes are associated with the severity of ICH. This may indicate potential goals for ICH therapy.

Keywords: CD4+/CD8+; ICH; lymphocyte; WBC

OPEN ACCESS

Correspondence:
Rajendra Shrestha, Department of Neurosurgery, NAMS, Bir Hospital, National Trauma Centre, Nepal, E-mail: rajendra39@yahoo.com

Received Date: *11 Feb 2019*
Accepted Date: *12 Apr 2019*
Published Date: *16 Apr 2019*

Citation:
Shrestha R, Pradhan R, You C. Immunological Changes Observed in ICH. World J Surg Surgical Res. 2019; 2: 1119.

Introduction

An intracerebral hemorrhage is also called hemorrhagic stroke, or "brain attack". It is one of the utmost terrified forms of neurological disease that not only causes significant morbidity and mortality but also results in poor socioeconomic outcome. It can occur at any age. It is slightly more common in men than in women. The central nervous system is reflecting its structure, metabolism and function one of the most complex bodily organs. It is the key system controlling and coordinating entirely important functions of the organism. As a result of ICH, disorders of the complete metabolic system happen. There is impairment of cellular immunological disorders occurring in ICH, but they do affect in an important way the course of the disease. That's why ICH patients are susceptible for infections. The occurrence of systemic infections after ICH may be a symptom of impaired immune competence [1]. Although the current era has implemented many novel innovations in nearly every aspect of management of this disease, the neurological result has still not changed significantly. In this study, we revealed that the presence of immunodepression in ICH patients, with its consequences in terms of bacterial infections aggravating the clinical course.

Materials and Methods

Sixty patients of both sexes with spontaneous intracranial hemorrhage were admitted consecutively and qualified for the study from May 2013 to Oct 2013 in the cerebrovascular hypertensive Unit of Neurosurgery Department of the "West China Hospital, Sichuan University". This study was approved by the Committee of Ethics in Research of the Neurosurgery department, West China Hospital, Sichuan University. All patients or their next of kin were given written informed consent. The diagnosis of spontaneous ICH was established by physical findings and brain

Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI). The ICH volume was measured from the first CT or MRI scan using a × b × c × 0.5 methods (Figure 1-3). For irregular shapes, the different formula a × b × c × 0.33 was used [2,3]. At admission to the hospital, the patients exclusively in patients with ICH for clinical and prognostic assessment. Patients or their legal representatives signed the informed consent for participation in the study. Basic clinical parameters, history of hypertension and previous antihypertensive therapy were included in the analysis. All the patients were followed until discharged from hospital. Before discharge they were also evaluated by the prognostic Glasgow scale.

The inclusion criteria included those ICH patients who were older than 18 years and non-pregnant, with no immune or endocrine disorders and not suffering from any active infectious disease or a non-aneurysmal ischemic disease. They should not have received any prior chronic glucocorticoid treatment or any hormonal contraceptives in the last 3 months. They should not have received any blood or massive electrolyte infusions during the hospital stay. They should not be malnourished and should not have any associated systemic diseases, such as renal, heart, respiratory failure and diabetes mellitus.

The study excluded Subarachnoid hemorrhage cases, patients classified in severe GCS score who refused operation, patients previously using drugs like replacement hormonal therapy of any type, having hemorrhages secondary to trauma, hemorrhages due to malformations, coagulopathy, and tumors, hematological disorders and cases of infection within the first 72 h.

Venous blood samples were obtained at 3 times: during the first 24 h of ICH that is at hospital admission (t0), 5 days (t1), and 10 days (t2). Blood samples were collected between 8 AM and 9 AM, within 24 h from ictus, centrifuged at 3000 rpm, for 10 min, and the serum stored at –20°C until assayed. Lymphocytes sublets CD3+, CD4+, CD8+, and CD4+/CD8+ were measured by Flow Cytometry (FCM). Flow cytometry was performed on the BD FACS CANTO™ flow cytometer (Becton Dickinson Corporation, New Jersey, USA). The reagent cocktail (10 µl) containing CD4-Flurescein Isothiocyanate (FITC), CD8-Phycoerythrin (PE) and CD3-Peridinin-Chlorophyll-Protein (PerCP) (Becton Dickinson Corporation, New Jersey, USA) were added to 50 µl heparin anticoagulated whole blood, and the samples were mixed and incubated for 30 min at room temperature. Erythrocytes were lysed by adding 450 µl of ammonium chloride haemolysis agent for 15 min. The lymphocytes were gated as forward-scattered light and side-scattered light. IgG, IgA, IgM, IgE and IgD determined with scattered turbidimetry. WBC and total lymphocyte were measured by fluorescent nucleic acid stains and flow cytometry (XE-5000, SYSMEX Company, Japan).

Data were analyzed by the Analysis of the Variance (ANOVA) and paired simple T-test for comparisons. Bivariate analysis was performed to investigate the correlates each other. The level of significance was fixed at $p<0.05$. The results were presented as mean ± standard deviation (M ± SD) with help of the Statistical Package for Social Sciences (SPSS) for Windows, version 21.0 (Chicago, IL).

Results

Twenty one patients managed conservatively, whereas thirty nine patients were symptomatic presenting with acute focal neurological deficits with mass effect on admission. Those significant patients were under gone surgical intervention. Eight patients were classified in mild group, forty seven in moderate group (9 to 12) and only five in severe grade (8 or lower) of the Glasgow coma scale (13 to 15).

Table 1: Glasgow come scale of admitted patients.

GCS	Frequency	Percent
Mild	8	13.3
Moderate	47	78.3
Severe	5	8.3
Total	60	100

Table 2: The relation of WBC, IgG, IgA, IgM, IgE, CD4, CD8, and CD4/CD8 in both patients by One Way ANOVA statistic.

Types	"0" day	"5 days"	"10 days"	P value
WBC	12.4 ± 3.1	12.1 ± 3.5	9.6 ± 3.6	<0.001
IgG	11.5 ± 3.4	11.7 ± 3	12.8 ± 3.7	0.129
IgA	1951.1 ± 942.9	2062.1 ± 945.9	2273.4 ± 779.5	0.231
IgM	1085.1 ± 492.9	1135.2 ± 458.1	1407.5 ± 437.7	0.005
Ig E	128.7 ± 185.8	213.8 ± 449.4	105.9 ± 110.1	0.19
CD4	28.8 ± 5.6	26.3 ± 8.1	34.6 ± 6.7	<0.001
CD8	21.1 ± 4	17.1 ± 4.2	21.3 ± 3.6	<0.001
CD/CD8	1.4 ± 0.4	1.6 ± 0.5	1.7 ± 0.5	0.031
Total protein	63.3 ± 9.9	61.8 ± 7.9	63.2 ± 7.9	0.56

Table 3: The relation of WBC, Lymphocyte, CD4, in the operative and conservative patients by paired sample T-test.

Types	Operation	Conservative	P value
WBC0	13.1 ± 3.3	10.9 ± 2.3	0.011
WBC1	13 ± 3.4	8.9 ± 1.5	<0.001
WBC2	10.2 ± 3.5	7.6 ± 1.7	0.001
Lymphocyte0	0.8 ± 0.07	1.4 ± 0.6	<0.001
Lymphocyte1	0.5 ± 0.2	1.7 ± 0.6	<0.001
Lymphocyte2	0.4 ± 0.2	1.9 ± 0.6	<0.001
CD4 0	27.9 ± 6.5	31.3 ± 4.3	0.039
CD4 1	22.2 ± 7.7	33.7 ± 5.3	<0.001
CD4 2	32.5 ± 5.9	39.7 ± 5.2	0.001

Immunological changes in peripheral blood of ICH patients

There were significant group differences were observed for leucocyte count, lymphocytes sublets CD4, CD8, and CD4/CD8 ratio at hospital admission (t0), 5 days (t1), and 10 days (t2) in both operative and conservative patients. WBC, lymphocyte count and CD4 count were statistically significate ($P<0.05$) at hospital admission (t0), 5 days (t1), and 10 days (t2) (Table 1-3). Leucocyte counts were elevated notice during time of admission due to an increased number of granulocytes. But those parameters were gradually altered on 5 days to 7 days of admission and normalized after full course of treatment in both surgical and conservative management cases (Chart 1). Operative patients showed significantly lower counts of CD4 T cells as early as day 5 days after acute ICH, compared to conservative patients. CD4+ T cell counts improved more quickly in patients who non operative patients compared with patients assigned to the operation. Furthermore, operative patients showed a persistent reduction in CD4 T cells at 5 days, whereas these parameters gradually normalized 10 days and over the follow-up period. This result directed important role of WBC and CD4 to recover in operatively

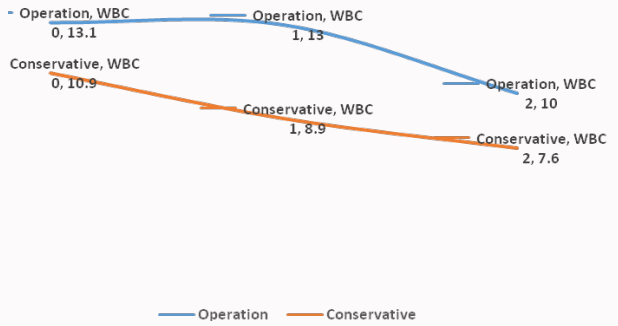


Chart 1: Line Chart is showing trends of WBC in at hospital admission (0), 5 days (1), and 10 days (2).

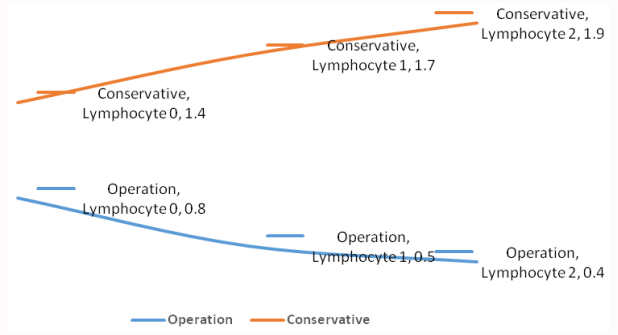


Chart 2: Line Chart is displaying trends of lymphocyte during hospital admission (0 days), 5 days (1), and 10 days (2).

and conservatively manage cases.

Immunoglobin in peripheral blood of ICH patients

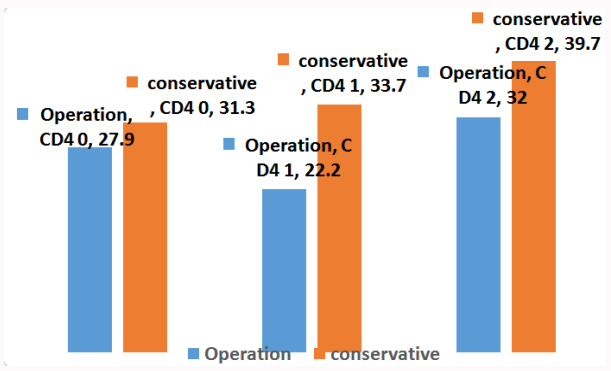
IgG, IgA, IgE and IgD levels were similar in conservative group and operative group. There were not significantly changes in between those groups. IgM was statistically significant (P<0.05) at hospital admission (t0), 5 days (t1), and 10 days (t2). There were no significant in younger group and older group (P>0.05).

Lymphopenia was noticeable in Patients

During the first day of admission after the onset of disease distinct changes of cell-mediated immunity were demonstrated as a decrease in total lymphocyte count in the peripheral blood. Lymphopenia was gradually noticed in operative cases and lymphocyte count was increasing into normal level in non-operative cases (Chart 2).

Correlations among different parameters were found. There were significant positive correlations between leukocyte with GCS (r=0.29, 0.30), Volume (r=0.21, 0.37) ICH score (r=0.35, 0.55) and mRS (r=-0.30, 0.47) during admission and discharge time respectively (p<0.05). But Leucocyte was negative correlation with CD4(r = -0.80, -0.45) and IGM (r = -0.10, -0.14) at hospital admission and discharge respectively. There were negative correlations between CD 4 with GCS (r = -0.28, -0.34), volume of hematoma (r = -0.23, -0.56), ICH score (r = -0.42, -0.47, mRS (r =-0.38, -0.46) during admission and discharge time (p<0.05).

There were significant incidence of chest infection, wound infections, meningitis (CSF infections), and urinary tract infections in intensive care patients. Chest infection, however, was significantly more frequent in operative patients (n=5 *vs.* n=0) after ICH. As causative agents, *staphylococcus aureus*, *haemophilus influenza*, and *Streptococcus pneumonia* were recognized. Interestingly,



Graph 1: Clustered column Chart is presenting trends of CD4 during hospital admission (0 days), 5 days (1), and 10 days (2).

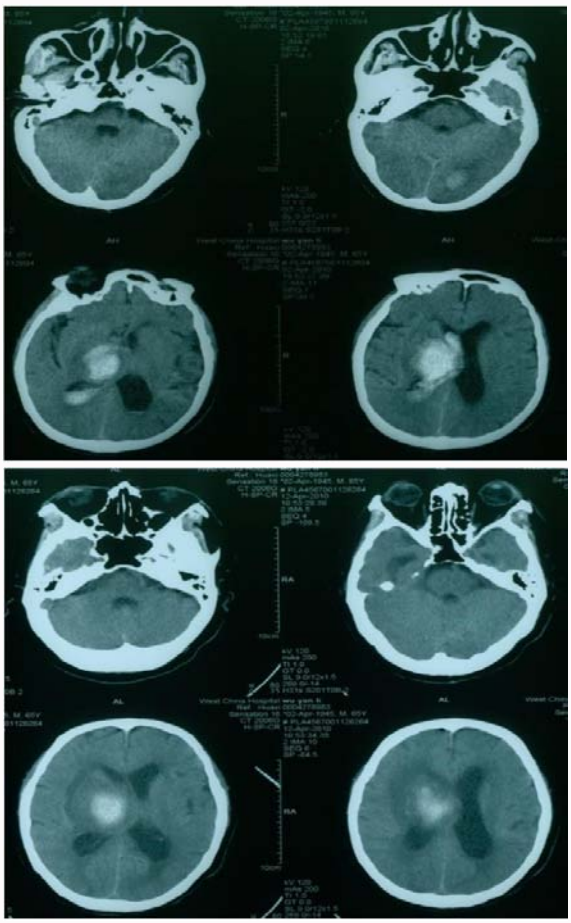


Figure 1: CT scan (First) of Case IV (65years/M) explaining right ICH managed conservatively. Post-admitted CT scan (second) of Case IV (65years/M) displaying hematoma well absorbed after 8 days.

patients with pneumonia had significantly lower T-cell counts and lymphocyte sublets production compared to non-infected patients as early as days 3 and 4 after ICH, respectively. Outcome of operative ICH patients was significantly impaired compared to the conservative group. Five patients died due to pneumonia followed by multi-organ failure and acute respiratory distress syndrome with fatal pulmonary insufficiency at days 17, 20, 21, 25 and 35 after ICH respectively.

Discussion

Spontaneous Intracerebral Hemorrhage (ICH) is leading cause of

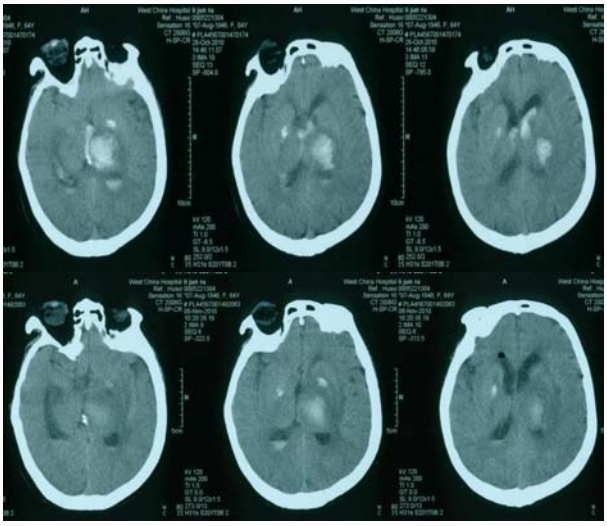


Figure 2: Preoperative CT scan (Above) of Case V (46/F) indicating left ICH with ventricle extension on admission and managed by burr hole drainage. Post-operative CT scan (Below) of Case II (46/F) showing hematoma almost disappeared.

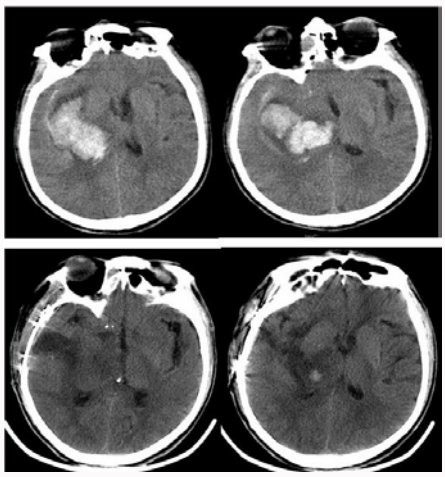


Figure 3: Pre-Operative CT scans (Above) of Case VI (62 years/male) found right intracranial hemorrhage with a midline shift. The hyper dense (bright) area represents acute bleeding .There is a midline shift to the patient's left. Post-operative CT scans (Below) of Case I (62 years/male) showing evacuation of hematoma.

high mortality and morbidity all over the world. In ICH, there is rapid accumulation of blood within brain parenchyma leads to increased intracranial pressure and interruption of normal structure. Significant tissue damage occurs quickly because of space occupying lesion and toxicity of the degrading hematoma. Secondary consequences of ICH include (1) cytotoxicity of blood, (2) excite toxicity, (3) oxidative stress and inflammation (4) hyper metabolism, (5) spreading depression [4-8]. After ICH the extravasated blood components (primarily erythrocytes and plasma proteins) and the "Damage" Associated Molecular Patterns (DAMPs), including nucleic acids, extra cellular matrix components, proteins, lipid mediators, ATP and uric acid released from necrotic and damaged tissue, impose a strong cytotoxic, pro-oxidative and pro inflammatory insult toward surrounding viable brain cells, and could be seen as early as minutes after onset of ICH. At this early stage the toxicity of extravasated blood plasma components including blood derived coagulation factors, complement components, immunoglobulins and other bioactive molecules are proposed to act as contributors to ICH affected tissue damage. Subsequently, Red Blood Cell (RBC) lysis starts at approximately 24 h and continues for the next several days, leading to discharge of cytotoxic Hemoglobin (Hb) with further deterioration of the pathological status. Ultimately, this pathogenesis leads to irreversible disruption of the components of the neurovascular unit, constituting gray and white matter, and is followed by blood-brain-barrier disruption [9-12].

Our study focused to judge the presence of immunodepression in acute ICH patients. Peripheral blood CD3+, CD4+, CD8+, Leucocytes and lymphocytes count are a marker of the response of the immune system and reflect the activation of the inflammatory cascade following a spontaneous ICH [13]. These are commonly practicable biomarker. Our study pointed that the presence of immunodepression was in ICH patients with its consequences in terms of bacterial infections complicating the clinical course. There are two most important findings: (1) ICH induced immunodepression occurred over high grades or operated cases; and (2) bacterial pneumonia occurred only in operative patients. Leukocytosis and lymphopenia were revealed in all ICH patients of our studies (Graph 1). The alteration in the leukocyte count and lymphocytes over 72 h may better reflect the amount of inflammatory response mounted in reaction to the ICH. In our studies, patients with clinical signs and symptoms of infection, including altered mental status, temperature, admission leukocyte count, abdominal pain, cough, burning urine or diarrhea underwent an infectious work up. Earlier studies had documented that raise peripheral leukocyte counts were associated with early neurologic deterioration but were not independently associated with functional outcomes as measured by modified rankin scale at 30 days. One recent study found that although a higher white blood cell count was associated with increased mortality in ICH patients, but this did not increase the risk of death independently of other indicators of ICH severity [14]. But our studies demonstrated their association with ICH volume and infection rate.

To our knowledge, this study is the first to prove immunodepression in relation to the acute ICH. These results suggested that the severity of disease combined with the clinical course to be strongly associated with the duration of immunodepression and occurrence of fever and pneumonia. In severe patients, we found a persistent suppression of the cellular immune response throughout the observation period of 10 days, whereas in medically manage patients parameters of immune competence recovered within 5 days after acute ICH. This is also reflected clinically because observation patients showed no signs of systemic inflammation and a lower incidence of fever as compared to the operative group. In the literature, Temporary immunodepression had been already defined in patients after acute traumatic brain injury and ischemic stroke. Comparable to our results, distinct immunodepression and severe infections occurred in post-operative ICH patients with serious clinical course. Clinical studies and experimental have directed that activation of the neurohumoral stress pathways that is the sympathetic nervous system and the hypothalamic pituitary adrenal axis, plays an important role in the inhibition of immune function after acute central nervous system injury [15,16]. It must likely similar mechanisms are applied in the development of immune depression after ICH.

Our study indicated that ICH induced immunodepression syndrome. However, the underlying pathophysiology remains unclear. Interestingly, we revealed that leukocytosis and lymphopenia

are associated with higher frequency of infections independently of ICH blood volume. We also found a strong relationship between intra ventricular hemorrhage extension, sympathetic activation and immunodepression. In ICH, intraventricular blood in the area of autonomic and immune controlling centers such as thalamus, hypothalamus may play a crucial role in sympathetic activation and, thus, in subsequent immune depression. There is increasing evidence that brain immune interactions become deregulated after ICH, resulting in a stroke related immunosuppression syndrome. ICH related blood brain barrier damage accelerates the interaction of immunocompetent blood cells with astrocytes, the facultative antigen presenting cells in the brain. Consequences may contain: (1) loss of some auto reactive lymphocyte clones due to adhesion to arterial walls, (2) trapping of lymphocytes in the places of their differentiation and maturation, and (3) bothered differentiation of lymphocyte progenitors [17]. These results show that marked changes are observed in cell mediated immunity shortly after ICH. They are manifested as a decrease in the total lymphocyte count, decrease in the T-lymphocyte population and lowering of immunoglobin and production of the leucocyte migration inhibition factor. The cause of the kind of changes is not clear. Little is known about immunological status of our patients before admission to hospital. They did not have evident symptoms of infection during the first examination at hospital. All of them were at home before the ICH. There was no active tuberculosis or neoplasia or others. Most of the patients in our studied groups had hypertension, but these appeared unlikely causes of such profound changes in the lymphocyte count and T-lymphocyte sublets. Our studied couldn't suppose that the immunological changes are a result of the advanced age of the patients as our medium age was 53 years. It is known that cell mediated immunity decreases with age [18,19]. In our control group healthy older subjects had a diminished cell mediated immunity as compared with younger persons, but changes in immunity in the older subjects were never so marked as in patients with strokes.

It is more likely that stroke alone leads very rapidly to changes in the immunological parameters. In our patients the immune depression may have been caused by stress induced severe alteration in the blood circulation and tissue destruction. It is recognized that stress induced by several factors can alter the immune response (Monjan and Collector 1977; Eskola et al.). Disorders in the metabolism of carbohydrates and amino acids known to happen in stroke can also change the immune reactivity. In cases of surgical injury and head trauma, the amount of brain dysfunction plays a role in the depression of the immune system. The reduction in cell-mediated immunity was maximum profound in cases with cerebral hemorrhage [20-22]. Very rapid and marked depression of cell-mediated immunity has been observed in patients after surgical operation (Graph 1). The decrease in the immune response was greater if trauma was more severe. Likewise, phagocytic activity also reduced in cerebrovascular accident which was dependent on the duration of loss of consciousness and severity of the tissue damage (Dodsworth and Harris 1971, Van Woerkom et al. 1973, 1977). Head trauma without proof of obvious tissue destruction, but only with loss of consciousness also leads to a decrease in the proportion of the peripheral blood T-lymphocytes and to impairment of their function [14,23].

We supposed that the depression in the immune function was caused by severe stress during the course of disease. Impairment of the immune function may increase susceptibility to infection. The humoral immune response was not so evidently changed, and the observed increase of IgM in the sera was probably present before the stroke. Etiology of raise IgM could not explant here. Experimental models of ischemic stroke and research in humans have well recognized stroke induced immune deficiency facilitated *via*. Hypothalamic pituitary axis and sympathetic nervous system activation. Catecholamine intervened impairment of cellular immune responses include lymphopenia, decreased lymphocyte activation, shift from Th1 to Th2 cytokine predominance, or decreased HLA-DR expression on monocytes [24]. Accordingly, higher sympathetic activity with subsequent inhibited immune function has been associated with the occurrence of posts ICH infections. High infection rate after severe stroke may partly relate to brain induced immunodepression syndrome. Acute stroke is susceptible to bacterial infection. Pulmonary and urinary infections are the leading medical problems after stroke and the leading cause of death, with prevalence of up to 33%. In an experimental stroke model, Sarrafzadeh et al. had revealed that cerebral ischemia induces a rapid suppression of cellular immune responses, which precedes the development of systemic bacterial infections within 3 days after stroke. The pathophysiological mechanisms leading to high incidence of infections after stroke are not fully explained. Dysphagia, impaired consciousness, aspiration caused by feeding tube placement, orotracheal intubation, reduced bulbar reflexes, and or mechanical ventilation for several days are considered to be major contributors to the high incidence of bacterial pneumonia after stroke [19,21,25]. It is therefore not shocking that this complication occurred only in symptomatic patients of our study. However, recent experimental and clinical studies stress the role of an impaired immune response in addition to neurological deficits causing dysphagia for the increased susceptibility to nosocomial pneumonia in patients with acute central nervous system injury [26]. We demonstrate in this study that patients with pneumonia showed significantly lower T-cell counts, rapid decrease in peripheral blood lymphocyte counts compared to patients without infectious complications. Notably, impaired cellular immune function in patients with pneumonia (particularly T-lymphopenia and leukocytosis) was evident as early as day 1 after ICH. This supports the conception that immunodepression after acute central nervous system injury is an additional risk factor that increases susceptibility to infections. Our results established that such kind of immunological changes forecasts outcomes after ICH and also addressed in time to minimize morbidity and mortality. This study clearly demonstrated the association between the peripheral immune response and poor functional outcomes after ICH independent of infection or hemorrhage size. However, none of these current treatments have made a significant impact on patient outcome. Mortality and morbidity have not changed in several decades, despite improvements in ICU care. This study provides further evidence for the potential of targeting neuroinflammation as a treatment modality to improve outcomes amongst ICH survivors.

Conclusion

WBC, lymphocytes, IgM and CD4 were significant ($P<0.05$) in both operative and conservative ICH patients. They were altered according to severity. Their counts can be used to forecast prognosis and opportunistic infections. Our study recommended addressing that ICH induced immunodepression syndrome. This will be an early and easily affordable parameter to detect patients at high risk of subsequent infection. This study is the first to prove immunodepression in relation to the acute ICH.

References

1. Meisel A, Meisel C. Stroke-induced immunodepression: Consequences, mechanisms and therapeutic implications. Future Neurol. 2008;3(5):551.
2. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke. 1996;27(8):1304-5.
3. Huttner HB, Steiner T, Hartmann M, Kohrmann M, Juettler E, Mueller S, et al. Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke. 2006;37(2):404-8.
4. Wagner KR, Sharp FR, Ardizzone TD, Lu A, Clark JF. Heme and iron metabolism: Role in cerebral hemorrhage. J Cereb Blood Flow Metab. 2003;23(6):629-52.
5. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. Lancet Neurol. 2006;5(1):53-63.
6. Ardizzone TD, Lu A, Wagner KR, Tang Y, Ran R, Sharp FR. Glutamate receptor blockade attenuates glucose hypermetabolism in perihematomal brain after experimental intracerebral hemorrhage in rat. Stroke. 2004;35(11):2587-91.
7. Qureshi AI, Ali Z, Suri MF, Shuaib A, Baker G, Todd K, et al. Extracellular glutamate and other amino acids in experimental intracerebral hemorrhage: An in vivo microdialysis study. Crit Care Med. 2003;31(5):1482-9.
8. Mun-Bryce S, Wilkerson AC, Papuashvili N, Okada YC. Recurring episodes of spreading depression are spontaneously elicited by an intracerebral hemorrhage in the swine. Brain Res. 2001;888(2):248-55.
9. Tang J, Liu J, Zhou C, Ostanin D, Grisham MB, Neil Granger D, et al. Role of nadph oxidase in the brain injury of intracerebral hemorrhage. J Neurochem. 2005;94:1342-50.
10. Wang J, Dore S. Inflammation after intracerebral hemorrhage. J Cereb Blood Flow Metab. 2007;27(5):894-908.
11. Wu J, Hua Y, Keep RF, Nakamura T, Hoff JT, Xi G. Iron and iron-handling proteins in the brain after intracerebral hemorrhage. Stroke. 2003;34(12):2964-9.
12. Zhao X, Song S, Sun G, Strong R, Zhang J, Grotta JC, et al. Neuroprotective role of haptoglobin after intracerebral hemorrhage. J Neurosci. 2009;29(50):15819-27.
13. Wekerle H, Linington C, Lassmann H, Meyermann R. Cellular immune reactivity within the CNS. Trends Neurosci. 1986;9:271-7.
14. Dirnagl U, Klehmet J, Braun JS, Harms H, Meisel C, Ziemssen T, et al. Stroke-induced immunodepression: experimental evidence and clinical relevance. Stroke. 2007;38(Suppl 2):770-3.
15. Mills PJ, Ziegler MG, Rehman J, Maisel AS. Catecholamines, catecholamine receptors, cell adhesion molecules, and acute stressor-related changes in cellular immunity. Adv Pharmacol. 1998;42:587-90.
16. Weller I, Lockwood CM, Chandra RK. Secondary immunodeficiency. In: Roitt I, Brostoff J, Male D, editors. Immunology, 5th ed. London: Mosby, 1998:293300
17. Prass K, Meisel C, Hoflich C, Braun J, Halle E, Wolf T, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by post-stroke T helper cell type 1-like immunostimulation. J Exp Med. 2003;198(5):725-36.
18. Kawaharada M, Urasawa K. Immunological functions and clinical course of elderly patients with cerebrovascular diseases. Nippon Ronen IgakkaiZasshi. 1992;29(9):652-60.
19. Klehmet J, Harms H, Richter M, Prass K, Volk HD, Dirnagl U, et al. Stroke-induced immunodepression and post-stroke infections: lessons from the preventive antibacterial therapy in stroke trial. Neuroscience. 2009;158(3):1184-93.
20. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. Neurology. 2003;60(4):620-5.
21. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci. 2005;6(10):775-86.
22. Asadullah K, Woiciechowsky C, Docke WD, Liebenthal C, Wauer H, Kox W, et al. Immunodepression following neurosurgical procedures. Crit Care Med. 1995;23(12):1976-83.
23. Vogelgesang A, Grunwald U, Langner S, Jack R, Bro¨ker BM, Kessler C, et al. Analysis of lymphocyte subsets in patients with stroke and their influence on infection after stroke. Stroke. 2008;39(1):237-41.
24. Chamorro A, Urra X, Planas AM. Infection after acute ischemic stroke: a manifestation of brain-induced immunodepression. Stroke. 2007;38(3):1097-103.
25. Perry L, Love CP. Screening for dysphagia and aspiration in acute stroke: a systematic review. Dysphagia. 2001;16(1):7-18.