NeuroRehabilitation 42 (2018) 449–456
DOI:10.3233/NRE-172362
IOS Press

Inflammation and rehabilitation outcomes in patients with nontraumatic intracranial haemorrhage

Mirella Boselli[a,1,*], Roberto Aquilani[b,1], Roberto Maestri[c], Maria Pia Achilli[a], Nadia Arrigoni[a], Evasio Pasini[d], Anna Maria Condino[e], Federica Boschi[e], Maurizia Dossena[b], Daniela Buonocore[b] and Manuela Verri[b]

[a]*Unità di Riabilitazione Neuromotoria Gravi Cerebrolesioni Acquisite, Istituti Clinici Scientifici Maugeri Spa Società Benefit, IRCCS Montescano, Pavia, Italy*

[b]*Dipartimento di Biologia e Biotecnologie "Lazzaro Spallanzani" Università degli Studi di Pavia, Pavia, Italy*

[c]*Dipartimento di Ingegneria Biomedica, Istituti Clinici Scientifici Maugeri Spa Società Benefit, IRCCS Montescano, Pavia, Italy*

[d]*Divisione di Riabilitazione Cardiaca, Istituti Clinici Scientifici Maugeri, IRCCS Lumezzane, Brescia, Italy*

[e]*Dipartimento di Scienze del Farmaco, Università degli Studi di Pavia, Pavia, Italy*

Abstract.

BACKGROUND: Systemic inflammation and its impact on rehabilitation for patients with non-traumatic haemorrhagic injury (HBI) sequelae has not yet been adequately documented.

OBJECTIVE AND METHODS: We therefore considered 31 patients with HBI, to determine the serum levels of inflammatory markers (C-Reactive Protein, CRP and or interleukine-6, IL-6) to establish their impact on functional status (Functional Independence Measure, FIM: 18 indicating the worst performance and 126, a normal score).

RESULTS: The results showed an inflammation prevalence (CRP >0.5 mg/dl and/or IL 6 >7 pg/ml) of 74.2% at admission to Rehab. FIM reduction was more pronounced in inflamed compared to non-inflamed subjects ($p < 0.05$) and significantly correlated with blood variables sensitive to inflammation, such as alpha 1 globulin ($r = –0.565$) and neutrophil/ lymphocyte ratio ($r = –0.52$), CRP ($r = –0.365$). At discharge from Rehab, the inflammation rate diminished. Inflamed patients showed similar gains in FIM score as their controls. In the entire population, the FIM gain was significantly associated with a gain in serum albumin, only ($r = +0.56$).

CONCLUSIONS: We conclude that systemic inflammation is prevalent in HBI patients and contributes to reduce patient functional status. However, during the Rehab stage, inflammation does not hinder the improvement rate of functional capacity.

Keywords: Haemorrhagic stroke, inflammation, rehabilitation, functional recovery rate

1. Introduction

Despite considerable advances in the diagnosis and treatment of hemorrhagic strokes, outcomes relative to death and disability remain poor (Mathers et al., 2000; American Heart Association, 1996). For physical disability, 59% of patients with subarachnoid haemorrhage (SAH) have a poor outcome at 3 months after the acute event (Badjatia et al., 2010). Early studies have found total disability in about 15% of patients with SAH, and moderate/good recovery in 20–35% of patients with hemorrhagic brain-injury (HBI) (Rosenørn et al., 1987; Säveland et al., 1986). In survivors, the severity of both brain and clinical

[1]M. Boselli and R. Aquilani contributed equally to this work.

*Address for correspondence: Manuela Verri, PhD, Dipartimento di Biologia e Biotecnologie "Lazzaro Spallanzani", Università degli Studi di Pavia, Via Ferrata 9, 27100 Pavia, Italy. Tel.: +39 0382 986423; Fax: +39 0382 986385; E-mail: manuela.verri@unipv.it.

damage during acute HBI, are important causal factors of reduced physical autonomy. Indeed, the acute event primes intracranial and systemic inflammatory response syndrome (SIRS), (Vila et al., 2000; Leira et al., 2004; Silva et al., 2005) which adds to systemic and intracranial pathophysiological processes (i.e., elevated intracranial pressure, reduced cerebral blood flow, decreased tissue oxygen supply, decreased total systemic blood flow) (Daverat et al., 1991).

Similar to ischemic strokes, HBI inflammation predicts early neurological deterioration (Leira et al., 2004). Of particular importance, plasma pro-inflammatory cytokines (TNFα, IL6) in subjects with HBI are associated with subsequent hematoma enlargement (Silva et al., 2005). The problem is that inflammation is particularly prevalent in acute strokes. Indeed, it develops in 59% of SAH patients admitted to intensive care unit (ICU) (Yoshimoto et al., 2001) and may also develop in up to 85% of the patients during their first 4 days of ICU stay (Dhar & Diringer, 2008).

Today, it has not yet been documented whether a possible persistence of inflammation in subacute (>3 weeks after acute events) patients negatively influences long-term functional recovery. This is crucial for the rehabilitation outcome of HBI subjects, as inflammation can potentially be manipulated by metabolic (Aquilani et al., 2015), drug or neurophysiological (vagal stimulation) interventions. As a result, the objective of this retrospective study conducted on rehabilitation subjects with HBI, was to investigate both the prevalence of residual systemic inflammation and its impact on patient recovery of functional independence.

2. Patients and methods

2.1. Patient selection

For this retrospective study, the medical records of patients with sequelae of HBI admitted to the rehabilitation unit (Rehab) of the Montescano Institute (Pavia Italy) from January 2014 to March 2016, were screened for study eligibility. Review and subsequent analysis criteria for selection included the diagnosis of non-traumatic HBI (intra-cerebral, intra-ventricular, sub-aracnoid haemorrhage), direct patient transfer from ICU to Rehab with the intent of reducing as much as possible, the high clinical heterogeneity of these patients. Subjects with concomitant pregnancy, previous episodes of cerebrovascular accident, malignancies, or who were following corticosteroid therapy and who were aged <18 years were all excluded.

2.2. Methods

Additionally, the subjects complying with our inclusion criteria needed to have performed a complete cycle of rehabilitation therapy as well as being measured for the following variables, both on admission to and discharge from Rehab:

1. Anthropometric characteristics: body weight (BW, Kg), body mass index (BMI,Kg/m^2), pre-event (habitual) BW. Habitual and actual (at admission to Rehab) BW served to calculate the loss of BW: actual BW/habitual BW <95% was considered an indicator of under-nutrition (Aquilani et al., 1999).
2. Bio-humoral measurements:

   a) Routine variables, including serum protein electrophoresis. White blood cell counts, neutrophil and monocyte counts were used as non-specific indicators of inflammation. Circulating neutrophil/lymphocyte ratio (normal value in our laboratory being 1.5–3) was considered an expression of inflammatory-immune activity (Aquilani et al., 2015).
   b) Markers of body inflammatory state:
      b1) serum levels of cytokine interleukine-6 (IL-6) (normal value <7pg/mL) (Aquilani et al., 2014a)
      b2) C-reactive protein (CRP; normal value <0.5 mg/dL) (Aquilani et al., 2014a)
   c) Serum proteins of acute phase response to the disease:
      c1) Positive reactants:
         ◦ α_1 globulin system (normal values 210–350 mg/dL)
         ◦ Fibrinogen (normal values 250–500 mg/dL).
      c2) Negative reactants:
      ◦ Albumin (normal values 4.02–4.76 g/dL)
      ◦ Prealbumin (normal values 20–30 mg/dL).

3. Functional status:

The patients' functional state was evaluated using the functional independence measure (FIM), as reported elsewhere (Boselli et al., 2012). Briefly, this test is an 18-item scale that measures patient independence in feeding, grooming, dressing, toileting,

mobility and cognition. A score of 126 indicates complete functional independence.

4. Nutritional intake:

Nutritional intake was evaluated by 3-day alimentary diary in self-feeding patients (Aquilani et al., 2014b) and calculated for patients on enteral nutrition from nutritional composition reported in the formula label.

5. Rehabilitation therapy:

Treatment was adapted to each individual patient. Briefly, rehabilitation consisted of therapeutic exercise with a personal physiotherapist for 60 minutes, five days a week. Exercise included passive, active and active-assistive range of motion exercise, coordination, facilitation techniques of the contro-lateral limbs, trunk exercise, active exercise of the unaffected limbs and ambulation with assistive devices or support. The number or repetitions in walking exercise distance was increased as the physical performance of each patient progressed. Speech therapy, neuropsychological rehabilitation, occupational therapy (daily living activities, vocational, perceptual and functional activity training) and recreational activity were also performed depending on individual needs.

2.3. Statistical analysis

Descriptive statistics were carried out for all recorded variables, reporting means and standard deviations for quantitative variables and distribution frequencies for qualitative variables. Chi square test was used for categorical variables. Repeated measurement of variance was used to assess any differences in trends over time between patients, with or without inflammation. Baseline differences between patients with inflammation and patient without inflammation were tested by unpaired Student *t*-test. The Mann-Whitney test was adopted for the non uniform distribution of values.

The FIM was correlated to biohumoral variables. Pearson or Spearman correlation coefficients were estimated at both admission to and discharge from the Rehab. Linear multiple regression analyses were performed in order to point out the variables with high association with FIM. Statistical significance was set at $p < 0.05$.

3. Results

Forty-two individuals with HBI were screened for the study. Eleven were excluded because of their provenience from settings other than ICU. As a result, thirty-one subjects were eligible for the study and were analyzed. Nine subjects were on enteral nutrition (29%) and 22 (71%) had oral alimentation.

Table 1 reports the demographic-, anthropometric-, clinical-, biohumoral-, nutritional-, functional characteristics of the entire population, both at discharge from ICU/admission to Rehab and at discharge from the Rehab institute.

At discharge from ICU/admission to Rehab (Table 2), a large majority of patients (74.2%) showed a persistence of mild systemic inflammation as indicated by serum IL-6, CRP levels above normal serum concentrations, which was significantly higher ($p < 0.05$ both) than in non-inflamed (25.8%) patients. In addition, erithrocyte sedimentation rate (ESR), white blood cell count, neutrophil and monocyte counts, neutrophil/ lymphocyte ratio (N/L) were all significantly higher in inflamed patients. Inflammation was associated with increased amounts of circulating positive proteins of the acute phase response (α1 globulin, fibrinogen) and respectively, decreased levels of negative ones (albumin, prealbumin). The inflamed patients were mildly under-nourished (actual BW <95% of habitual BW), whereas non-inflamed subjects were not. Patients as an entire population had important reductions in their functional independence (FIM), (Table 1) but this reduction was more pronounced in inflamed subjects ($p < 0.05$) (Table 2).

Functional independence negatively correlated with serum α1-globulin ($r = -0.565$, $p = 0.0007$), N/L ratio ($r = -0.52$, $p = 0.002$), neutrophils ($r = -0.47$, $p = 0.01$), serum CRP ($r = -0.365$, $p = 0.01$) and positively linked to albumin ($r = 0.43$, $p = 0.008$). At regression analysis, α1-globulin ($p < 0.01$), N/L ratio ($p = 0.05$) and albumin ($p = 0.02$) remained significantly correlated with FIM.

At discharge from Rehab, (Table 2), all inflammation indicators in inflamed subjects decreased, although CRP and IL-6 did not normalize. Even given these molecules were not different from non-inflamed subjects, they did indicate the permanence of residual inflammation. Coherently, circulating proteins of acute phase response improved with reductions of positive reactants and the increase of negative ones. In more detail, the fibrinogen concentration of inflamed group, compared to that in non-inflamed one

Table 1
Demographic, clinical, anthropometric, biohumoral and nutritional variables in the haemorragic stroke population both at admission to and discharge from Rehab

Variables	Entire population ($n = 31$)		%RDA	p values
	Admission to Rehab	Discharge from Rehab		
Demographic:				
Male/Female	14/17		–	
Age (years)	60.29 ± 14.62		–	
Haemorrage aetiology				
Intracerebral haemorrage:				
Intraparenchimal haemorrage	19 (61.3%)		–	
Aneurismatic subaracnoid haemorrage:	12 (38.7%)		–	
Anthropometric				
Actual body weight (Kg)	65.69 ± 16.51	66.96 ± 16.05	–	ns
Body mass index (BMI) (Kg/m2)	23.67 ± 4.95	24.02 ± 4.91	–	ns
Pre-event body weight (Kg)	71.00 ± 20.55			
Actual/pre-event body weight	0.94 ± 0.06	0.95 ± 0.06	–	ns
Blood				
ESR 1st hour (mm) (nv: <20)	47.29 ± 31.06	25.96 ± 21.98	–	0.0016 (**)
Haemoglobin (g/dl) (nv: 12–15)	11.66 ± 1.82	12.39 ± 1.65	–	0.0013 (**)
Blood urea (mg/dl) (nv: 20–40)	39.74 ± 25.40	33.23 ± 12.49	–	0.0996 (ns)
Serum creatinine (mg/dl) (nv: 0.7–1.2)	0.84 ± 0.30	0.85 ± 0.26	–	0.4704 (ns)
Plasma glucose (mg/dl) (nv: 80–110)	107.06 ± 33.30	91.20 ± 18.25		0.018 (*)
Interleukin-6 (IL-6) (pg/ml) (nv: <7)	18.65 ± 27.48	9.86 ± 12.09	–	0.06 (ns)
Serum C-reactive protein (CRP) (mg/dl) (nv: <0.3)	2.19 ± 2.83	1.31 ± 2.55	–	0.1285 (ns)
Serum Fibrinogen (mg/dl) (nv: 350–495)	395.88 ± 83.37	360.05 ± 63.37	–	0.0394 (*)
α1 globulin (g/dl) (nv: 0.21–0.35)	0.33 ± 0.16	0.27 ± 0.14	–	0.0431 (*)
Serum albumin (g/dl) (nv: 4.02–4.76)	3.16 ± 0.59	3.53 ± 0.65	–	<0.0001 (***)
Serum prealbumin (mg/dl) (nv: 18–30)	19.88 ± 5.50	22.09 ± 6.55	–	0.0295 (*)
Daily nutritional intake				
Energy			–	
Kcal	1755 ± 327			
Kcal/Kg (nv: ≥25)	26.7 ± 5.8		100	
Proteins				
g	62 ± 8.6			
g/Kg (nv: ≥1)	0.94 ± 0.37		97	
Lipids				
g	63 ± 7.2			
g/Kg (nv: ≤1)	0.96 ± 0.7		92	
Carbohydrates				
g (nv: 140–180)	235 ± 65		127.7	
g/Kg (nv: 2.5–4)	3.57 ± 0.98			
Functional state:				
FIM score (nv: 18–126)	38.71 ± 21.19	64.58 ± 29.59		<0.0001 (***)

Data are expressed as mean ± standard deviation (SD). ESR, erytrocyte sedimentation rate; FIM, functional indipendence measure; ns, not significant; nv: normal values; RDA, recommended daily allowance. Statistical analysis: Paired t-test between the same group at admission to and at discharge from Rehab ($p < 0.05$).

significantly decreased over time. In the inflamed group, the blood glucose significantly changed.

The patients as an entire population, (see Table 1) improved their functional independence by about a score of 25.9. The gains in FIM (ΔFIM) were similar for both inflamed (+28.1) and non-inflamed (+19.5) subjects ($p = 0.2$). The results moreover, showed that 54.8% of the HBI patients did not reach the minimum gain of +22 score FIM (Beninato et al., 2006), which was considered clinically significant (Aquilani et al., 2014b). In these patients, the ΔFIM was 9.35 ± 6.58 scores, quite unlike the ΔFIM of subjects (45.2%) with ΔFIM ≥22 scores (+45.93 ± 19.17 scores; $p < 0.0001$). During rehabilitation, improvements in functional independence of the patient population were linked to improvements of circulating albumin only (ΔFIM vs Δalbumin $r = +0.56$, $p = 0.0005$).

4. Discussion

The study showed that at discharge from ICU, the prevalence of residual inflammation among subjects with HBI can reach significant levels, thus contributing to patient disability. However, during

Table 2
Anthropometric, biohumoral and functional indipendence measured in subjects with CRP ≥0.5 (inflamed) or with CRP <0.5 (No-inflamed) at admission to and discharge from Rehab

Variables	Inflamed ($n=23$)		NO Inflamed ($n=8$)		Trend over time (p level) interaction
	Admission	Discharge	Admission	Discharge	
Anthropometric					
Actual body weight (Kg)	66.41 ± 17.45	66.76 ± 17.63	63.63 ± 14.29	67.57 ± 11.09	ns
Actual/pre-event body weight	0.94 ± 0.06	0.93 ± 0.06	0.96 ± 0.06	0.99 ± 0.03	ns
Blood					
ESR 1st hour (mm)	54.10 ± 32.23*	28.5 ± 25.36	26.86 ± 15.20	19.43 ± 6.35	ns
Haemoglobin (g/dl)	11.37 ± 1.72	12.12 ± 1.73	12.49 ± 1.96	13.84 ± 1.04	ns
Blood urea (mg/dl)	41.3 ± 28.05	32.7 ± 10.71	35.25 ± 16.18	35.00 ± 18.12	ns
Serum creatinine (mg/dl)	0.84 ± 0.3	0.81 ± 0.24	0.85 ± 0.34	0.97 ± 0.33	ns
Plasma glucose (mg/dl)	110.35 ± 35.72	89.67 ± 16.04	97.63 ± 24.61	95.14 ± 24.06	0.03
Blood white cell count (n/mm3)	7919.55 ± 1792.77**	6572.38 ± 2744.5	5721.43 ± 2348.46	5081.43 ± 1031.72	ns
of which:					
Neutrophils(%)	65.02 ± 9.92**	59.20 ± 8.67	58.87 ± 9.05	55.37 ± 11.31	ns
Lymphocytes (%)	23.05 ± 8.15	28.39 ± 8.76	31.13 ± 9.38	34.16 ± 10.83	ns
Monocytes (%))	8.35 ± 2.62*	9.08 ± 2.60	7.73 ± 1.50	7.96 ± 0.86	ns
Neutrophils/Lymphocytes rate	3.34 ± 1.76*	2.50 ± 1.56	2.08 ± 0.77	1.83 ± 0.8	ns
α1 globulin (g/dl)	0.38 ± 0.16**	0.30 ± 0.15	0.19 ± 0.05	0.18 ± 0.02	ns
Serum albumin (g/dl)	3.01 ± 0.56**	3.38 ± 0.66	3.58 ± 0.49	4.02 ± 0.26	ns
Serum prealbumin (mg/dl)	18.37 ± 4.35**	19.59 ± 4.82	24.24 ± 6.38	29.24 ± 5.63	ns
Interleukin-6 (IL-6) (pg/ml)	17.5 ± 11.20*	11.96 ± 13.84	6.21 ± 4.46	4.63 ± 1.45	ns
Serum Fibrinogen (mg/dl)	412.47 ± 85.59*	366.94 ± 71.44	332.8 ± 26.85	341.67 ± 31.63	0.04
Serum C-reactive protein (CRP) (mg/dl)	2.93 ± 3.02**	1.65 ± 2.88	0.25 ± 0.16	0.28 ± 0.32	ns
Functional state					
FIM score	35.39 ± 18.23	63.48 ± 31.02	48.25 ± 27.18	67.75 ± 26.70	ns

Data are expressed as mean ± standard deviation (SD). ESR, erytrocyte sedimentation rate; FIM, functional indipendence measure. Statistical analysis: Unpaired t-Test between the two groups at admission to Rehab *$p<0.05$; **$p<0.001$. Repeated analysis of variance measurements to compare the variable trends over time between inflamed and non-inflamed patients.

the rehabilitation stage of the disease, residual inflammation does not seem to hinder patient recovery of functional independence given that both, inflamed and non-inflamed subjects had similar opportunity to retrieve their physical capacity rate.

1) Inflammation and functional independence

a) At discharge from ICU/admission to Rehab

Disease severity (Badjatia et al., 2010), neurological interventions (Esper et al., 2006) and infection complications (Esper et al., 2006; Iadecola & Anrather, 2011) during ICU-stay are probably the major factors responsible for the persistence of inflammation at patient discharge from ICU. At this stage of the disease, inflammation was mild and accounted for alterations of circulating proteins, both positive and negative, of the acute phase response. The fact that α1-globulin and peripheral inflammatory neutrophils and monocytes where high, might suggest the persistence of inflammatory processes in the damaged brain area at about 30 days after the acute event. This agrees with pathological studies showing an inflammatory infiltrate in the lesioned brain area that persists for years after any stroke (Iadecola & Anrather, 2011). On the other hand, a high N/L ratio indicates a prevalence of inflammatory activities over the adaptive immunity and repair processes (el-Hag & Clark, 1987). This is reinforced by the finding of increased α1-globulin concentrations, which indicates increased levels of the anti-protease system, which in turn limits protease overproduction/ activity of neutrophils and monocytes primed by the inflamed brain area (Iadecola & Anrather, 2011). Inflammation probably impacts the development of patient disability, as the FIM score was lower in inflamed compared to non-inflamed ones, and various indicators of inflammation negatively correlated with FIM. The relationship between α1-globulin and functional independence was also found in subjects with cerebral ischemia (Aquilani et al., 2014a).

b) At discharge from Rehab

During rehabilitation, the inflammation rate declined but protein changes of the acute phase response remained, even if they were attenu-

ated. Reduced inflammation was associated with functional independence improvement, similar to non-inflamed subjects. In inflamed subjects, the reduced inflammation created a better blood glucose concentration, suggesting improved cell glucose metabolism.

This study cannot explain the similar gains of functional independence between inflamed and non-inflamed subjects. A potential explanation could be the ambivalent activity of inflammation, which on one hand is detrimental to the injured brain although at the same time, may also favour brain repair (Aquilani et al., 2014a). Indeed, inflammatory cytokines have concomitant anti-inflammatory properties as they down-regulate inflammatory tumour necrosis factor-α (TNF-α) and IL-1 (Zoico & Roubenoff, 2002) and induce the production of anti-inflammatory glucocorticoids (Chang & Bistrian, 1998). The pro-inflammatory IL-6, increased in our inflamed patients, exerts direct neuroprotection activities and regulates learning and memory process by influencing both nerve cell regeneration after injury (Chang & Bistrian, 1998) and neuronal differentiation (Kishimoto, 1989), increasing secretion of neurotrophic factor by astrocytes (Kishimoto, 1989). Indeed, the IL-6 is highly expressed in the hippocampus (Bliss & Collingridge, 1993) cerebral cortex (Kirkwood et al., 1995), amygdale (Stevens, 1998) and all structure involved in cognitive processes.

Thus, the mild increase of IL-6, observed here, may have played a role in inducing neuroprotection explaining in this way the improvement rate of FIM in inflamed subjects. On the other hand, normalized circulating phagocytic cells and N/L ratio, associated with improved FIM, would suggests that during the rehabilitation stage of HBI, the repair processes in the brain's damaged area probably prevailed over inflammatory ones (adaptive brain remodelling).

Trends towards normalization of liver synthesis of proteins of acute phase response, is of great clinical importance, given that any gain of functional independence was linked to the improvement the supply of albumin. Therefore, patient recovery of functional capacities appears to depend upon, both the reduction of inflammation, leading to a prevalence of adaptive immunity (repair processes), and on increases in circulating albumin. Interestingly, a correlation between overtime changes in albumin and in functional independence was also found in individuals with sub-acute cerebral ischemia (Aquilani et al., 2014a).

2) Circulating albumin levels and functional recovery

The albumin contribution to improving post-HBI recovery of brain functioning should not be underestimated for at least two reasons. Firstly, hypo-albuminemia may be caused not only by inflammation but also due to a patient's inadequate protein-calorie intake, a condition which can easily be manipulated. Secondly, albumin exerts important neuroprotection activity.

Inadequate protein-calorie intake frequently occurs in both acute (Davalos et al., 1996; Davis et al., 2004) and subacute (Aquilani et al., 1999, 2008a) stroke and conditions the clinical (Davalos et al., 1996; Davis et al., 2004) and functional prognoses of patients (Aquilani et al., 2008a, b). Liver albumin synthesis may also be impaired in cases of alterations in plasma amino acid profile (Aquilani et al., 2014b). It has been documented that adequate protein/ amino acid intake exerts direct action on neuronal survival (Doutheil et al., 1999) and neuro-cognitive recovery of subjects with ischemic stroke (Aquilani et al., 2008a, 2010). The mild undernutrition state of our inflamed patients, showed at admission to, and at discharge from Rehab, would suggest that patient protein-energy intake was not optimal and could limit the improvement of liver albumin synthesis due to reduced inflammation. Moreover, inadequate protein energy intake may also have contributed to lower serum prealbumin.

The important direct neuroprotection exerted by albumin has been established in several studies showing that human albumin therapy provides neuroprotection in transient focal ischemia (Belayev et al., 1997, 1998, 2001) global ischemia (Belayev et al., 1999) and traumatic brain injury (Ginsberg et al., 2001). As a result, sub-optimal protein energy intake and therefore, lack of albumin improvement could limit brain repair, which could in turn contribute to explain why most patients did not achieve the minimum FIM gain ($\geq$22 scores) translating into clinical advantage to patients (Beninato et al., 2006), and why mean FIM gain in patients with increased FIM $\geq$22 scores was only 45. We speculate that intensive rehabilitation therapy, when not accompanied with optimal nutritional metabolic conditions, may not be enough to achieve better rehabilitation outcomes. This could explain the loss of physical autonomy of our study patients. The disability rate was 60% in subjects with ΔFIM <22, and 37.5% in those with ΔFIM $\geq$22. This study would suggest that

optimized protein/amino acid intake, timely improvements of circulating albumin and modulation of neuro-inflammation (el-Hag & Clark, 1987) could all be useful tools to enhance rehabilitation outcomes. These issues, doubtlessly require further well-planned investigation. An additional suggestion from this study is that these interventions should be initiated from the moment the patients are accepted into ICU.

5. Conclusions

This study shows that the prevalence of a residual inflammation was shown to be high in subjects with non-traumatic cerebral haemorrhage at discharge from ICUs, contributing to the patient disability rate. Its reduction during rehabilitation, would favour patient functional capacity recovery.

5.1. Limitations of this study

We recognize that this study has several limitations. As a retrospective investigation, we cannot definitely establish the specific role played by inflammation in determining the level of patient disability or functional recovery. For this aim, a well planned interventional investigation targeting the reduction of inflammation with subsequent impact on patient autonomy would be needed. The measurements both at admission to ICU and Rehab of several cytokines including the anti-inflammatory IL-10 and the pro-inflammatory IL-17 (Iadecola & Anrather, 2011) would be useful to understand the balance between pro- and anti- inflammatory state better, mainly their time courses and impact on functional ability.

Acknowledgments

The authors would like to thank Prof. Robert Coates (Centro Linguistico, Bocconi University, P.zale Sarfatti, Milano, Italy), medical writer and editor, for his linguistic revision.

Conflict of interest

All authors declare no conflicts of interest.

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