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Chitotriosidase Activity in Cerebrospinal Fluid of Traumatic Brain Injury Patients: Relationship to Neuroinflammation and Outcome

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1. Abstract

The enzyme Chitotriosidase (Chit) has been used as a marker of macrophage activation, given its high value in plasma of patients with strong phagocytic activity. Intrathecal neuroinflammation has been reported in traumatic brain injury (TBI) and described to persist for days or weeks in humans.

1.1. Methods: In this study we established whether Chit activity is increased in cerebrospinal fluid (CSF) of TBI patients. The association with cytokine production in CSF and the correlation with the Glasgow Outcome Scale Extended (GOSE) at 6 months post-trauma was also analysed.

1.2. Results: Our results confirm that the increase of the Chit levels in CSF of patients with TBI is associated with an improved level of inflammatory cytokines (IL1 ß and TNF-α) and correlates with GOSE outcome scores at 6 months post-injury.

1.3. Conclusions: The correlation between Chit activity and the prognosis of brain trauma open the way to future works, in larger patient sample size, and suggests to use Chit as a prognostic biomarker of TBI.

2. Introduction

The human chitotriosidase (Chit) belongs to the glycoside hydrolase family 18 and is highly secreted by fully activated mononuclear cells of all tissues and, to a lesser extent, by peripheral polymorphonuclear leukocytes [1]. Little is known about the physiological role of Chit, although it has been demonstrated that it hydrolyses chitin, a structural and functional component of many insects and pathogens [2]. Changes in Chit activity has been found in plasma of normal individuals and in patients with a mutation in exon 10 of CHIT1 gene, causing an asymptomatic Chit activity deficiency [3, 4]. Pathophysiological implications of the enzyme deficiency are not well understood. In normal individuals, Chit activity has been identified as a marker of macrophage activation. In fact, patients with chronic conditions accompanied by significant phagocyte activity, such as the lysosomal Gaucher's and Niemann Pick's diseases [5], β-thalassemia [6] or atherosclerosis [7], and patients with acute and chronic parasitic infections, such as malaria and Leishmaniosis [8], show an elevated Chit activity in their plasma. Evidence of intrathecal Chit activity has been reported in Gaucher's disease [9], and preliminarily also in some chronic inflammatory neurological diseases such as stroke and multiple sclerosis [10, 11]. In traumatic brain injury (TBI), intrathecal glial activation, macrophage infiltration and increased cytokines production has been reported in both human and animal studies [12, 13]. In particular chronic glial activation has been associated with the progression of neurodegeneration [14].

Given the current lack of information on the impact of Chit activity in TBI and on the relationship of increased Chit with cerebral inflammation, in this work, we designed a study to assess Chit activity in cerebrospinal fluid (CSF) of patients with accidental brain

trauma. Correlations between Chit activity with some cytokines, measured in serial samples of CSF, were determined to establish the potential role of Chit as a parameter of neuroinflammation in the injured brain. Moreover, clinical parameters of initial injury were assessed using the Glasgow Coma Scale (GCS), the Injury Severity Score (ISS). Finally, we evaluated whether the intrathecal Chit activity is eligible as a prognostic marker for TBI by assessing correlations with the Glasgow Outcome Scale Extended (GOSE) at 6 months.

3. Material and Methods

3.1. Patient Selection

The study was conducted in accordance with the National Health and Medical Research Council of Australia National Statement on Ethical Conduct in Research Involving Humans and received prior approving by The Alfred Hospital Human Ethics Committee before commencement. Ten patients were recruited from the Trauma Service of the Alfred Hospital, Melbourne. Patients were included into the study on the basis of suffering severe TBI, established by a post-resuscitation pre-intubation Glasgow Coma Scale score (GCS) ≤ 9 and the requirement of an extra ventricular drain (EVD) for monitoring the intracranial pressure (ICP). Patients' management included preliminary computer tomography (CT) scans within 4 hours from the accident to assess the extent and classification of brain injury, followed by surgical implantation of an in situ intracranial pressure monitor coupled with an EVD. The CSF was drained when the ICP was greater than 20 mmHg and collected in bags over 24 hours in cooled containers at approximately 4˚C. CSF samples were collected daily for 6 days, beginning from the first 24 hours post-admission (day 0) up to day 5 after injury. Clinical data of patients are summarized in Table 1. Mean age was 28.7 years (range 16-47). Seven were males and three females. All CSF aliquots were stored at -80 C° until Chit activity determination was performed. In addition, 28 CSF samples from patients with other neurological disease (OND) were used as control: including trigeminal neuralgia (4 patients), headache (4 patients), cerebral venous thrombosis (4 patients), paraesthesia of undetermined origin (4 patients), amyotrophic lateral sclerosis (4 patients), alcoholic and other toxic polyneuropathies (4 patients), acute myelitis of undetermined origin (4 patients). Since increased Chit levels are reported in atherosclerotic and stroke patients [7-11], these two OND categories have been ruled out from our study. All patients and controls (or one of their relatives when that was not possible) gave informed consent, to participate in the study according to the Helsinki declaration.

3.2. Chit activity Assay

Measurement of enzymatic Chit activity was performed in duplicate, as already described, in both serial CSF patients and serum samples of TBI patients, over 6 days [13, 15]. Briefly, Chit activity was measured in CSF by incubating 30 µL of neat CSF with 100 mL of a solution containing 22 mM/L of the fluorogenic substrate 4-methylumbelliferyl-beta-D-N, N, N-triacetyl-chitotriose (Sigma Chemical Co.) in 0.5 M citrate phosphate buffer pH 5.2, for 15 min at 37°C, as originally described by Hollak et al. [15]. The reaction was stopped using 2 mL of 0.5 M/L Na2CO3 NaHCO3 buffer, pH 10.7. The fluorescence emission of the formed 4-methylumbelliferone was evaluated at 450 nm, using a Hitachi 2500 fluorimeter, adopting a 365 nm excitation wavelength. Chit activity was expressed as nanomoles of substrate hydrolyzed per millilitre per hour (nM/mL per h). This reaction was specific since both the effects of lysozyme, which has some catalytic activities, and another chitinase, acidic mammalian chitinase (AMcase), were excluded using this substrate. Moreover, the activity of each sample was found constant after repeated measurements. Patients with serum Chit activity below 2.5 nmol/mL/h were considered as Chit deficient.

Table 1: Patients clinical characteristics.

Patient	Age	Sex	Marshall Score	Contusion	GOSE	GCS	HYPO	HYPOXIA	MHAIS	ISS	TRISS
1	16	M	EML	A	3	3	3	1	5	29	87,6
2	19	M	DI 2	2,44	5	4	3	3	5	33	80
3	47	F	DI 2	2	1	1	3	3	5	43	68,7
4	33	M	EML	A	1	1	3	3	5	33	35,4
5	18	M	EML	A	3	3	3	1	5	15	80
6	35	F	DI2	2	5	4	3	3	5	20	75
7	20	M	EML	A	1	1	3	3	5	30	64
8	39	M	DI2	A	1	1	3	3	5	28	35
9	24	F	DI2	2.5	2.5	3	3	3	5	30	3
10	36	M	EML	A	1	1	3	3	5	25	80

GOSE (Glasgow Outcome Scale Extended): 1=Dead; 2=Vegetative State; 3=Lower Severe Disability; 4=Upper Severe Disability; 5=Lower Moderate Disability; 6=Upper Moderate Disability; 7=Lower Good Recovery; 8=Upper Good Recovery

GCS (Glasgow Coma Scale): severe TBI ≤ 8

ISS (Injury Severity Score): 0=no injury; 75= maximal injury

HYPO

MHAIS

ISS (Injury Severity Score): 0=nessun infortunio; 75= massima lesione

TRISS

3.3. Cytokines Determinations

The concentration of IL-6, IL-8, IL-10 and TNF-α was determined, using a Bio-Plex Cytokine Assay System (Bio-Rad, Sydney, Australia), in CSF and serum according to the manufacture instructions. In brief, samples (50 µl), standards and a mixture of cytokine antibody-coupled beads (50 µl) were added into a 96-well filter plate in duplicates, mixed and incubated overnight at 4°C. After removal of the incubation buffer and washing, a cocktail of biotinylated antibodies was added in each well to react with cytokines. Then, fluorescent tagged streptavidin (streptavidin-phycoerythrin) was added to form a fluorescent cytokine-antibody complex. The concentration of each cytokine was determined by a Bio-Plex Suspension Array System (Bio-Rad) that quantifies cytokines. Cytokine concentrations were automatically calculated by the Bio-Plex Manager software (Bio-Rad) using a calibrated curve derived from a recombinant cytokine standard. Samples from the same corresponding time points were used to assess both Chit and cytokine levels for each patient. IL-1β was measured by ELISA Kit in accordance to the manufacture instructions (R&D Systems).

4. Statistical Analysis

The data treatment was performed by using the SigmaStat 3.0 software. Chit activity values were not symmetrical distributed (Lorentzian instead of Gaussian) and for this reason the median and the interquartile range (IQR: 25° percentile or 1st quartile and 75° percentile or 3rd quartile) were used. The Mann Whitney Rank-Sum test for non-parametric variables and r Spearman correlation coefficient were used for statistical analysis; significance was conventionally established for P values <0.05. To better analyse the relation between the Chit activity and the GOSE score, a multiple linear regression analysis was carried out. A correlation analysis between the main variables (Chit in the CSF, ISS and GOSE at 6 months from brain trauma) was performed.

5. Results

5.1. Chit Activity and Cytokine Values in CSF Over 6 Days

The Chit activity and cytokines (IL-1β, TNF-α, IL-6, IL-8 and IL-10) were measured for the first time in TBI patients over 6 days every day and the values were reported in Table 2. The mean of these values shows a pick at 2 days and 4 days, due to ineffective attempt to reduce the macrophage activity. The median CSF Chit activity in TBI patients was 9 nM/ml/h (IQR 14.45-5.034) and 0.45 nM/ml/h in health controls (IQR 0.57-0.33), the difference being highly significant (Mann Whitney test, p<0.001). In addition, analysis of cytokines and their changes over time in CSF samples shows patterns similar to Chit changes over time with an initial increase and a later decrease.

Table 2. Levels of chitotriosidase (nMol/ml/h) and cytokines (pg/ml) in different days after TBI.

DAYS	1°	2°	3°	4°	5°	6°
Chitotriosidase	10,307	14,45	10,48	9,729	8,057	5,034
IL-1β	0-658	0-905	0-500	0-485	0-350	0-304
TNF-α	0.7-757	0.5-800	0-750	0-600	0-550	0-450
IL-6	140-35000	100-3000	0-3000	0-3300	0-3400	0-3500
IL-8	260-8000	200-2800	180-2000	150-2000	140-1500	145-1800
IL-10	0.5-440	0.5-400	0.4-380	0.3-350	0.4-380	0.4-380

5.2. Correlations of Chit with Clinical Parameters GCS, ISS and GOSE

TBI patients were stratified according to their GOSE score: from low to moderate (GOSE 0 - 3.5; 9/10 patients) and from moderate to severe disability (GOSE > 4; 1/10 patients). In Table 3 were reported Chit activity and values of several cytokines (IL-1β, TNF-α, IL-6, IL-8 and IL-10) in patients with lower GOSE, higher GOSE >4 and in controls. Chit activity was significantly lower in the group with lower GOSE (0 - 3.5) and higher in that with higher GOSE > 4. Furthermore, the initial GCS (at admission to Emergency) and the final follow-up GOSE score of the individual patients were correlated to the CSF Chit activity as shown in Figure 1. The correlation between Chit activity and GOSE was significant (p=0.0501) while the correlation between Chit and GCS was not significant. In this model, Chit total variability is explained by the variable GOSE at 6 months, which is the most statistically significant positive predictor of Chit (coefficient of determination R2 = 0.50176). In addition, a correlation was found among Chit activity and the expression of IL-1β (coefficient of determination R2 = 0.9845; Figure 2) and TNF-α (coefficient of determination R2 = 0.9438; Figure 3), while no correlation was found among the cytokines IL-6 and IL-10 (data not shown).

Table 3. Values of Chit (nMol/ml/hr) and cytokines (pg/ml) in CSF of patients with GOSE 0-3.5, GOSE ≥ 4 and Controls.

	GOSE 0-3.5	GOSE ≥ 4	Controls
Chitotriosidase	20	16	0.33
IL-1 β	0-700	0-400	0-380
TNF-α	0-800	0-500	0-400
IL-6	100-30000	0-3500	0-3000
IL-8	200-2800	180-2000	145-200
IL-10	0.5-500	0.3-350	0.4-300

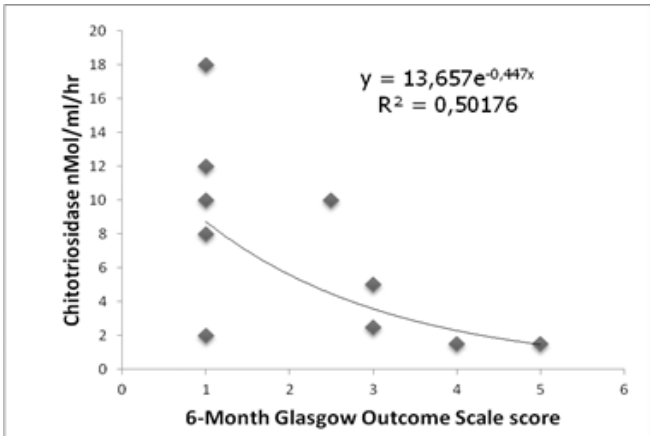

Figure 1: Correlation between Gose and CSF Chitotriosidase (nMol/ml/hr).

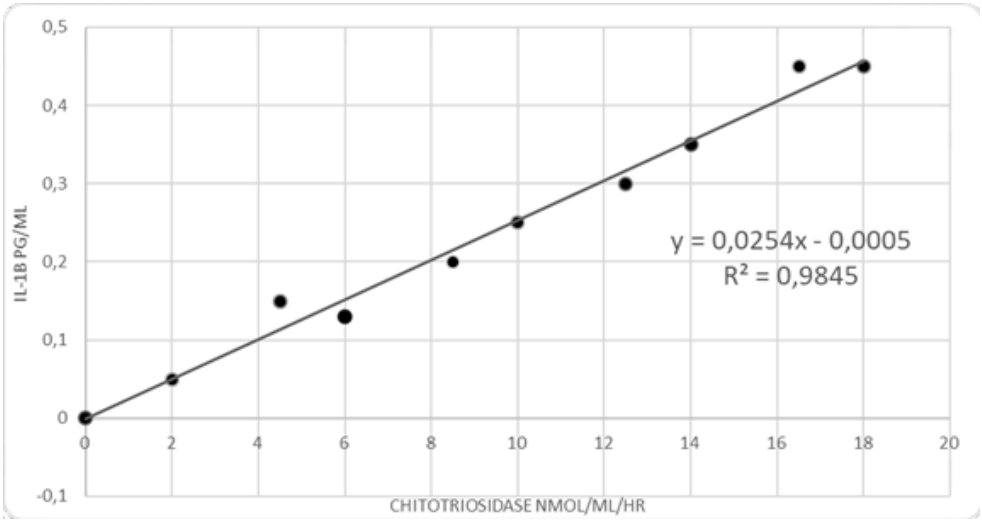

Figure 2: Correlation between Chit and IL-1ß.

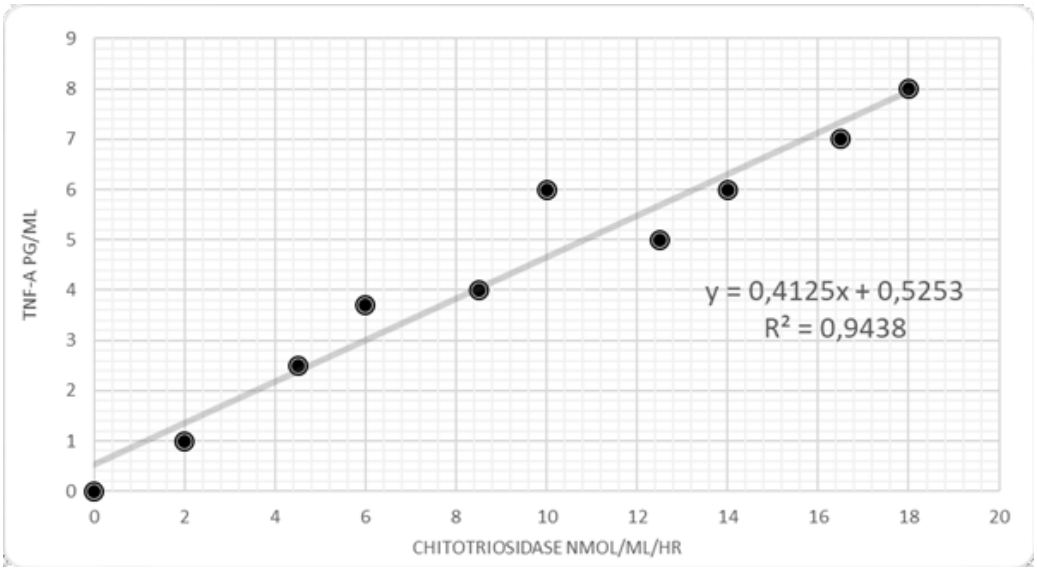

Figure 3: Correlation between Chit and TNF-α.

6. Discussion

Although cytokines play a role in the pathogenesis of neuroinflammation in brain trauma, there are several distinct reports on the controversial relationship between CSF cytokine levels and clinical outcome [13]. In fact, some researchers have reported that elevated concentrations of IL-1β and IL-6 in CSF of patients with brain trauma are associated with an unfavourable clinical outcome [16], while others did not report any correlation [17]. However, it is known that the inflammatory response induced by posttraumatic brain oedema creates secondary neuronal damage, which may be responsible of cognitive impairment such as epilepsy, depression and neurodegenerative disease [18]. Some studies have demonstrated that in new borns with asphyxia the macrophages show a role in the pathogenesis of brain damage [19]. In particular, level of quinolinic acid, a metabolite of kynurenine pathway, is dependent on neuroinflammation and is associated with cytokine response [20]. In an in vitro study we observed that Chit is expressed in reactive astrocytes when exposed to chitin or LPS in culture [21]. This data could link the increase of the Chit activity in CSF of patients with brain trauma accompanied by release of inflammatory cytokines [22]. Transcription of CHIT is also induced in reactive astrocytes, which are physiological constituents of local neuroinflammation, where gliosis occurs after TBI [23, 24].

Early increase of various cytokines in the brain, also reported in rat brain injury model, demonstrates that IL1-β, TNF-α, and IL6 reach the peak within few hours after brain injury and thereafter decline [24-26]. Using a rat model, it has been demonstrated that the activation of astrocytes at the site of injury corresponds to an acute inflammatory reaction, as measured by IL-1β protein production [25]. Consequentially, a decrease in macrophage stimulation and astrocytic reactivity may lead to the reduction in Chit expression and activity [27]. This could imply that cytokines up-regulated in the injured areas of the brain during the acute neuroinflammation may be responsible for astrocytic transcription of Chit. Neuroinflammation can persist for longer period and the role of glia and neuroinflammatory mediators, such as cytokines, can evolve with time from processes that perpetuate secondary injury to ones that facilitate cellular rescue and recovery [28, 29].

The role of Chit in reactive astrogliosis is still obscure, but data indicate that it may be involved in growth factor mobilization from the extracellular matrix. Isman et al. [26] investigated the time course(s) of Chit changes in patients with aneurysmal subarachnoid haemorrhage and showed that CSF and/or serum Chit levels might be used as a specific biomarker for disease severity. These results indicate that Chit activity is elevated in the acute stages of subarachnoid haemorrhage but is not a specific marker of disease severity. Recently Bonneh-Barkai et al. [30] assessed the utility of another chitinase YKL-40, chitin- and collagen-binding glycoprotein without chitinase activity, and member of "mammalian chitinase-like proteins", which was found elevated in CSF of patients with brain trauma. They suggest that YKL-40 could be considered as a temporal biomarker for reflecting pathophysiology and prognosis in such patients. In this study a significant correlation was found between mean YKL-40 and mean cytokines in CSF (IL-1β and TNF-α), while the association between IL-6 and IL-10 were not significant.

In this study we found a significant correlation between the average CSF Chit activity and IL-1 levels ($p=0.0001$) and TNF-α levels ($p=0.0001$). However, the correlations between IL-6 and IL-10 were not significant due to a possibly independent regulation [22, 31]. The association between Chit and cytokines implies that the higher Chit activity concentration is associated with a pro-inflammatory response (IL-1β) that may negatively influence the clinical outcome. In some of our patients, lower activity of Chit could be due to the presence of a subpopulation with Chit deficiency showing a marked reduction of chitinolitic activity [4]. Considering that Chit could be associated with brain trauma prognosis, future works with larger sample sizes should assess the significance of Chit measurement to assist the long-term outcome prediction after brain trauma. Based on this preliminary data, we generated a sample size calculation to determine the power of this sample data. This in order to obtain the number of subjects needed to show a significant relationship between Chit levels and neuroinflammation parameters at the beginning of trauma and at the end of observation. Despite differences in Chit levels were detected between patients with different GOSE score, a greatest sample of subjects is needed to reach significant differences with 80% of power. Finally, other studies may be able to support the role of plasma Chit activity as a biomarker in milder TBI where EDV placement and intracranial pressure management are not required.

7. Conclusion

This study suggests that elevation of Chit activity in CSF is associated with neuroinflammation and is strongly correlated with unfavourable outcome in TBI patients. After this initial analysis, further work is required to evaluate the utility of Chit as a biomarker of brain injury and the role of neuroinflammation in modulating Chit activation. Then, future studies may also be able to support the role of Chit as a biomarker in milder TBI, where EDV placement and intracranial pressure management are not required.

8. Competing Interests

The authors declare that they have no competing interest.

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