Original Research Article

CHANGESIN GFAP LEVELS BETWEEN PRE AND POST VENTRICULOPERITONEAL SHUNTS IN HYDROCEPHALUS PATIENTS

ABSTRACT

Introduction: Hydrocephalus is a disease that attacks the brain.Glial fibrillary acidicprotein (GFAP) is a structural cytoskeleton protein expressed by astroglial and neuronal stem cells. One of the hydrocephalus treatments is the VP Shunt. After the treatment through the VP Shunt procedure, GFAP levels generally change. This study aims to determine changes in serum GFAP levels before and after insertion surgery VP Shuntin hydrocephalus patients.
Methodology: This study was an analytic observational quantitative study with a cross-sectionalapproach. The research subjects were patients with hydrocephalus who were treated at the Neurosurgery Section of the Regional General Hospital Dr. Moewardi from April to June 2020.
Results and Discussion: This study had 14 subjects consisting of 9 (64.3%) male subjects and 5 (35.7%) female subjects. The median value of GFAP levels before treatment was 370.5 pg/mL with the lowest level of 168 pg/mL and the highest of 1734 pg/mL. The median value of GFAP levels after VP shunt action was 249.5 pg/mL with the lowest value of 137 pg/mL and the highest of 724 pg/mL. It was found that the GFAP level before and after the VP shunt action had a significant difference with $p = 0.035$ ($p<0.05$).
Conclusion: There is a significant difference between the GFAP serum levels before the action and after VP Shuntwas performedin hydrocephalus patients.

Keywords:Hydrocephalus, Glial fibrillary acidic protein (GFAP), VP Shunt

1. INTRODUCTION

Hydrocephalus is a disease that attacks the brain, which generally occurs in children. In hydrocephalus patients, there is an imbalance between the production of cerebrospinal fluid (CSF) and its absorption. CSF maintains intracranial pressure through reduced CSF by draining it outside the skull cavity by accelerating its flow through the various foramina, up to the venous sinus, or into the lumbar subarachnoid cavity which has about 30% of expansion capacity [1]. Glial Fibrillary Acidic Protein (GFAP) is a structural cytoskeleton protein expressed by astroglia and neuronal stem cells. If there is a brain injury, astroglia will react by producing more GFAP, which in turn will be released into the CNS fluid and blood. GFAP is thought to be produced exclusively by astrocytes, so this protein is specifically found in the brain. One of the hydrocephalus treatmentsis the VP Shunt. After the treatment through the VP Shunt procedure, GFAP levels generally change [2].

2. METHODOLOGY

This study was an analytic observational quantitative study with cross-sectionalapproach to determine changes in serum GFAP levels before and afterinsertion surgery VP Shuntin hydrocephalus patients(range of age 1-60 years old). The research subjects were patients with hydrocephalus who were treated at the Neurosurgery Section of the Regional General Hospital Dr. Moewardi from April to June 2020.Examination of GFAP levels were only performed twice, before and after surgery in each patient. Inclusion criteria in this study were hydrocephalus patient, diagnosed with CT scan, who provide informed consent and have plan for VP shunt. Patients with history of previous VP-shunt surgery, who had severe condition or died, and patients who had VP-shunt malfunction during observation were excluded. In this study, the data normality test was conducted first. The normality test of the sample distribution was carried out using the Shapiro-Wilk test. If the data is normally distributed, a different test will be performed using the dependent test or paired T-test. If the data is not normally distributed, an analysis will be carried out using theWilcoxon Test. Analyses were performed using Statistical Product and Service Solution (SPSS) for Windows.

3. RESULTS AND DISCUSSION

Subjects in this study were all hydrocephalus patients treated by the Neurosurgery section of the Regional General Hospital Dr. Moewardi Surakarta.Sampling was conducted from April to June 2020 by purposive random sampling. The number of research subjects was 14 patients whose blood serum was taken before and after the VP shunt procedure so that 28 blood samples were obtained to be analyzed for GFAP levels. The analysis of serum GFAP levels was carried out using the ELISA method. In all patients (100% of the study group) regardless of sex, age, place of residence or etiology, the doctors used surgical therapy.Patient characteristics were analyzed by univariate analysis, and differences in mean variables were analyzed using bivariate analysis ofdifference test of Wilcoxon Signed rankwith a significance value ($p < 0.05$).

This study had 14 subjects consisting of 9 (64.3%) male subjects and 5 (35.7%) female subjects. Blood serum samples were analyzed using the ELISA method. The median value of GFAP levels before treatment was 370.5 pg/mL with the lowest level of 168 pg/mL and the highest of 1734 pg/mL. After the patient underwent a VP shunt, a post-procedure blood serum sample was taken on the fourth post-treatment day. The median value of GFAP levels after VP shunt action was 249.5 pg/mL with the lowest value of 137 pg/mL and the highest of 724 pg/mL.

Table 1. Characteristics of Research Subjects

Variable		Description (n = 14)	*P-Value*
Gender	Male	9 (64.3%)	
	Female	5 (35.7%)	
GFAP levels Preoperative		370.5 (168 - 1734)	0.002
Post-operative GFAP levels		249.5 (137 - 724)	0.005

Table 2. Results of Wilcoxon Test Analysis GFAP Levels

	Median (Minimum - Maximum)	*P-Value*
Pre-VP Shunt Level	370.5 (168 - 1734)	0.035*
Post-VP Shunt Level	249.5 (137 - 724)	

**) p is significant if p < 0.05*

Analysis of the Shapiro-Wilk normality test showed that the pre-VP shunt and post-VP shunt GFAP data levels were not normally distributed ($p = 0.002$; $p = 0.005$). Table

2shows the results of the Wilcoxon test analysis for GFAP levels. The pre-treatment GFAP level had a median value of 370.5 pg/mL with the lowest level of 168 pg/mL and the highest of 1734 pg/mL. The median value of GFAP levels after VP shunt action was 249.5 pg/mL with the lowest value of 137 pg/mL and the highest of 724 pg/mL. After analyzing the difference test, it was found that the GFAP level before and after the VP shunt action had a significant difference with a p-value of 0.035. In fourteen study subjects, there was a decrease in GFAP levels on the fourth day of treatment after the VP shunt while 2 subjects experienced an increase in GFAP levels in the blood on the fourth day of treatment.

The purpose of the operative procedures is the reduction or normalization of increased intracranial pressure by removing the cause of disease, implanting a drainage system to provide constant draining of excess CSF from the ventricular system. Sociodemographic data (sex, age and place of residence) have no effect on the treatment of hydrocephalus in newborns. In all cases of hydrocephalus in the study, the treatment used was implantation of a drainage system [4].

It was found that 12 study subjects had decreased GFAP levels and 2 subjects experienced increased GFAP levels after VP shunt placement. This finding is supported by the research of Miller and McAllister stating that shunt implantation, both short and long terms, is effective in reducing the increase in GFAP due to hydrocephalus and causes a decrease in the presence of astrocytes and microglia as a whole [5]. Significantly increased levels of GFAP in hydrocephalus patients show an astrocytic response to elevated ICP. Astrogliosis is generally described as a specific reaction to brain damage and is accompanied by an increase in GFAP expression [3]. The amount of GFAP titer in plasma/blood serum correlates with the extent of brain damage. A significant increase in GFAP levels occurs 2 hours after the onset of ischemia and continues for up to 4 days [6].

Biomarkers can also be used to provide outcome prediction and risk triage. Current assessment tools include clinical characteristics (e.g., age, sex, reaction of the pupils, GCS score, and secondary insults), radiological data, and electroencephalography, which provide some predictive information. However, there are inherent limitations in these procedures. Clinical examinations are usually subjective and are often confounded by medications such as sedation, intubation/tracheostomy, and muscle relaxants, making them less reliable in the setting of the state-of-the-art critical management including hypothermia and early sedation. Head CT scanning, magnetic resonance imaging, or eletroencephalography often require specialized equipment or technical/interpretive expertise that may not be available at resource-limited medical centers. Further, they do not offer adequate information on the biochemical changes in the brain [7]. Thus, identification of valid neurobiochemical markers of brain injury that serve as surrogates of the presence, evolution, and outcomes of brain injury is key to the research and treatment of hydrocephalus patients.

GFAP is a specific marker (biomarker), an astrocyte intermediate protein [8] Furthermore, this is expressed in brain tissue injury and is a marker of the occurrence of astrocyte reactions (astrogliosis). Increased cerebrospinal fluid pressure in the ventricles causes atrophy of the white matter which will interfere with tissue perfusion resulting in local tissue hypoxia, damage to myelinated nerve pathways, and, finally, irreversible gliosis [9].

Glial fibrillary acidic protein (GFAP) is the hallmark intermediate filament (IF; also known as nanofilament) protein in astrocytes,a main type of glial cells in the central nervous system (CNS). Astrocytes have a range of control and homeostatic functions in health and disease. Astrocytes assume a reactive phenotype in acute CNS trauma, ischemia, and in neurodegenerative diseases. This coincides with an upregulation and rearrangement of the IFs, which form a highly complex system composed of GFAP(10 isoforms), vimentin, synemin, and nestin. This is evidenced by several studies showing

that GFAP will be expressed into blood plasma immediately after a brain injury occurs, and GFAP will not be expressed in patients with other trauma without brain injury. In the injured CNS, astrocytes will experience a reaction response called astrogliosis. Astrogliosis is characterized by rapid and profuse GFAP expression by astrocyte cells [9,10].

Glial fibrillary acidic protein (GFAP) gives strength and shape of cells on astrocytes. Glial fibrillary acidic protein found in the white and gray matter and in the upregulation of astrogliosis. Current data indicate that GFAP is an indicator of cell destruction.Cytoskeletal damage to neurons in the hydrocephalic process was found to be more prominent in the periventricular white matter axons than in the soma and cortical dendrites or in the axons of the internal capsule. The finding that axonal damage to the periventricular white matter represents the least complete recovery after shunt insertion may explain the impaired cognitive function seen in shunted children and appears to have reconstituted the brain mantle. The finding of GFAP-positive astrocytes reproducing around well-repaired axons in shunt-managed hydrocephalus may suggest that reactive astrocytes play a role in axonal recovery [9,11].

4. CONCLUSION

In this study, it was found that there is a significant difference between the GFAP serum levels before the action and after VP Shunt was performedin hydrocephalus patients at Regional General Hospital Dr. Moewardi, Surakarta.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient for publication of this research study. A copy of the written consent is available for review by the Institutional Review Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Health ResearchEthics Committee of Dr. Moewardi General Hospital (103/II/HREC/2021) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

REFERENCES

1. Aoyama Y, Kinoshita Y, Yokota A, Hamada T. Neuronal damage in hydrocephalus and its restoration by shunt insertion in experimental hydrocephalus: a study involving the neurofilament-immunostaining method. J Neurosurg. 2006 May;104(5 Suppl):332-9.
2. Beems T, Simons KS, Van Geel WJ, De Reus HP, Vos PE, Verbeek MM. Serum- and CSF-concentrations of brain specific proteins in hydrocephalus. Acta Neurochir (Wien). 2003 Jan;145(1):37-43.
3. Sivagnanam M and Jha NK. Hydrocephalus: An Overview, Hydrocephalus;2012.
4. Slusarz R, Rosińczuk-Tonderys J, Jabłońska R, Królikowska A, Kisiel A, Daniluk-Matraś I. Hydrocephalus in newborns: clinical conditions and primary surgical treatment. Adv Clin Exp Med. 2013 Mar-Apr;22(2):237-43.
5. Miller JM, McAllister JP 2nd. Reduction of astrogliosis and microgliosis by cerebrospinal fluid shunting in experimental hydrocephalus. Cerebrospinal Fluid Res. 2007 Jun 7;4:5.
6. de Oliveira AJM, Rossi J, Morales MNB, Reis BM, Pinto FCG. An unusual ventriculoperitoneal shunt complication: catheter migration into the breast. Autops Case Rep. 2020 Apr 2;10(2):e2020165.

7. Lei J, Gao G, Feng J, Jin Y, Wang C, Mao Q, Jiang J. Glial fibrillary acidic protein as a biomarker in severe traumatic brain injury patients: a prospective cohort study. Crit Care. 2015 Oct 12;19:362. doi: 10.1186/s13054-015-1081-8.
8. Yang Z, Wang KK. Glial fibrillary acidic protein: from intermediate filament assembly and gliosis to neurobiomarker. Trends Neurosci. 2015 Jun;38(6):364-74.
9. Žurek J, Fedora M. The usefulness of S100B, NSE, GFAP, NF-H, secretagogin and Hsp70 as a predictive biomarker of outcome in children with traumatic brain injury. Acta Neurochir (Wien). 2012 Jan;154(1):93-103; discussion 103.
10. Hol EM, Pekny M. Glial fibrillary acidic protein (GFAP) and the astrocyte intermediate filament system in diseases of the central nervous system. Curr Opin Cell Biol. 2015 Feb;32:121-30. doi: 10.1016/j.ceb.2015.02.004.
11. Hariyanto AS, Retnowati E, Turchan A. Serum glial fibrillary acidic protein levels profile in patients with severe traumatic brain injury. Indones J. Clinical Pathol. Med. 2017 Nov;24(1):24-28. doi: 10.24293/ijcpml.v24i1.1151.