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ORIGINAL ARTICLE

# Tumor necrosis factor alpha and interleukin-1 beta levels in cerebrospinal fluid examination for the diagnosis of ventriculoperitoneal shunt-related ventriculitis

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## Abstract

**Purpose** Ventriculitis is known to develop after chronic inflammation and bacterial invasion of the ventricular surface with a recurrence of shunt infections. The aim of this study is to evaluate the diagnostic value of elevation in cerebrospinal fluid (CSF) interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) together with CSF culture and laboratory test results in the diagnosis of ventriculoperitoneal (VP) shunt-related ventriculitis, which is known to be more problematic than conventional shunt infection.

**Methods** The study included a total of 34 patients with a VP shunt due to hydrocephalus, who presented with a headache, fever, and shunt infection at the Emergency Department and had a pre-diagnosis of ventriculitis. Nineteen patients were diagnosed with shunt-related infection or ventriculitis using the CSF obtained from the shunt pump. The IL-1β and TNF-α levels from the CSF samples of all patients were measured using the Micro ELISA immunoassay method.

**Results** CSF direct microscopic observation revealed that the mean cell count, IL-1β level, CRP level, and blood leukocyte level were higher in patients with ventriculitis compared to those diagnosed with shunt infection ($p = 0.02$, $p = 0.009$, $p = 0.004$, and $p = 0.009$, respectively). The probability of predicting positive culture outcome was 92.7% with 90.9% sensitivity and 82.6% specificity when IL-1β values exceeded 4.0 pg/ml. TNF-α values did not show a significant, reliable pattern compared to IL-1β.

**Conclusions** IL-1β is a reliable parameter which shall be used in the diagnosis of ventriculitis by predicting positive culture outcome with high sensitivity and specificity.

**Keywords** Shunt infections · Ventriculitis · TNF-α · IL-1β

## Introduction

Infections that develop after a ventriculoperitoneal (VP) shunt operation cause failure in hydrocephalus treatment.

Postoperative cerebrospinal fluid (CSF) infections are diseases with high mortality, morbidity, and cost; many factors contribute to these outcomes. Therefore, besides the necessity of early diagnosis and treatment, it is imperative to characterize the clinical setting clearly in the presence of infection, and the prevention of unnecessary antibiotic therapy or the decision of cessation of started antibiotic treatment are the increasingly essential parameters. These decisions are often not made easily with the indicators currently used.

Today, acute phase reactants, WBC (white blood cell) count, CRP (C-reactive protein), and ESR (erythrocyte sedimentation rate), which are used as infection parameters in the systemic inflammatory response, are not considered infection-specific indicators. Specific therapy involves the growth of the microorganism on the culture medium and administering the appropriate treatment. However, culture results that might be available within

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42–78 h and occasional observation of results consistent with contamination are the inconveniences that result in delayed treatment.

Ventriculitis associated with shunt infections has a characteristic infection pattern present on computerized tomography(CT) with ependymal contrast enhancement, an increase in the number of leukocytes in the cerebrospinal fluid (CSF) of > 100/mm$^3$, and an infection pattern in which culture reproduction is generally positive.

In addition, a substantial increase in the number of white blood cells (> 20,000), high CRP and erythrocyte sedimentation rates, a low CSF glucose ratio, and an IL-6 level of > 10 units/mL are noteworthy parameters [17, 23, 25, 26]. In cases where the proximal end of the shunt catheter is infected, infection is directly transmitted to the ventricular system and forms the clinical picture described above. In this situation, the duration of infection is lengthy and long-term intravenous (IV) and/or intraventricular antibiotic therapy is required because of treatment-resistant microorganisms [3, 14]. In cases of shunt infection, which are frequently encountered by pediatric emergency services, biochemical evaluation and CSF culture results are the parameters that shape treatment and determine the duration of therapy.

It is known that cytokines rapidly elevate at the time of inflammation and sustain the inflammatory process. Proinflammatory cytokines, such as interleukin 1-beta (IL-1β) and tumor necrosis factor alpha (TNF-α), increase in severe bacterial infections and sepsis.

In the literature, there are many studies on cytokines performed in patients with meningitis, in contrast to the few studies on ventriculitis patients [1, 4, 8, 12, 13, 16, 19, 30]. These studies were often performed on patients with external ventricular drainage. Since cytokines increase immediately upon the onset of inflammation and are released locally by immune cells during a bacterial infection, we investigated CSF cytokine values obtained from the ventricular system of patients admitted with shunt infection.

## Material–Method

Çukurova Medical Faculty's Ethics Committee approved this study, carried out in accordance with Helsinki's principles of Declaration. This study included patients with hydrocephalus who had undergone VP shunt surgery and were followed for external ventricular drainage at Çukurova University Faculty of Medicine Hospital between December 2012 and December 2013 with suspicion of ventriculitis. There was suspicion of VP shunt infection or ventriculitis in the patients who presented to the emergency department with symptoms clinically suggestive of shunt infection, such as fever or confusion, and in the patients who followed-up for external ventricular drainage. Shunt infection was diagnosed by medical history, physical examination, contrast-enhanced cranial CT imaging findings, and intraventricular CSF findings, including number and type of cells, protein and glucose levels, and CSF culture [15].

A total of 34 patients were enrolled in the study and divided into two groups, patient group ($n$ = 19) and control group ($n$ = 15). The patient group included the patients who were admitted to the emergency department and found to have shunt infection. The control group consisted of patients who did not have a finding suggestive of infection in the microscopic assessment of the CSF and reproduction in CSF microbiological culture. In the control group, six patients were diagnosed with intracranial mass and followed up for EVD due to acute hydrocephalus, and the remaining nine patients were diagnosed with shunt dysfunction without cells in the direct microscopic examination of the CSF and without reproduction in CSF culture. In the patient and control groups, 3 cc CSF sample was obtained from the shunt pump under sterile conditions after admission and direct examination, CSF levels of IL-1β and TNF-α, glucose, and protein levels in the CSF for biochemical evaluation; and WBC count, percentage of neutrophil and lymphocyte distribution, ESR, and CRP were analyzed and then routinely assessed. Ventriculitis was clinically diagnosed in the patients with symptoms of shunt infection, reproduction in microbiological culture, cells in CSF of > 100/mm$^3$ on direct microscopic examination, increased CRP and ESR levels, decreased glucose level in the CSF, and ependymal contrast enhancement on CT [15, 33]. Eleven patients fulfilled these criteria and diagnosed as ventriculitis (Fig. 1).

For the evaluation of the cytokines, CSF samples were stored at − 80 °C within 20 min after the sample collection and collectively examined at once. Results were obtained in 2 h with the micro Elisa immunoassay method; the samples were examined in the Central Laboratory, Faculty of Medicine, Çukurova University. (Biotek Instruments, Cloud-Clone Corp. USCNK).

### Statistical analysis

We used SPSS 17.0 software in the statistical analysis of the data. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as means and standard deviations (when necessary, median and minimum-maximum). In the intergroup comparison of the continuous variables, the distributions were controlled and, as the parameters did not show normal distribution, the Mann-Whitney $U$ test was used. In the study, in the patients with and without culture, cutoff values for IL-1β, ESR, and CRP were attempted to be determined by calculating the sensitivity and specificity and by investigating the area under the ROC curve. In all tests, the statistical significance level was considered to be 0.05 Table 1.

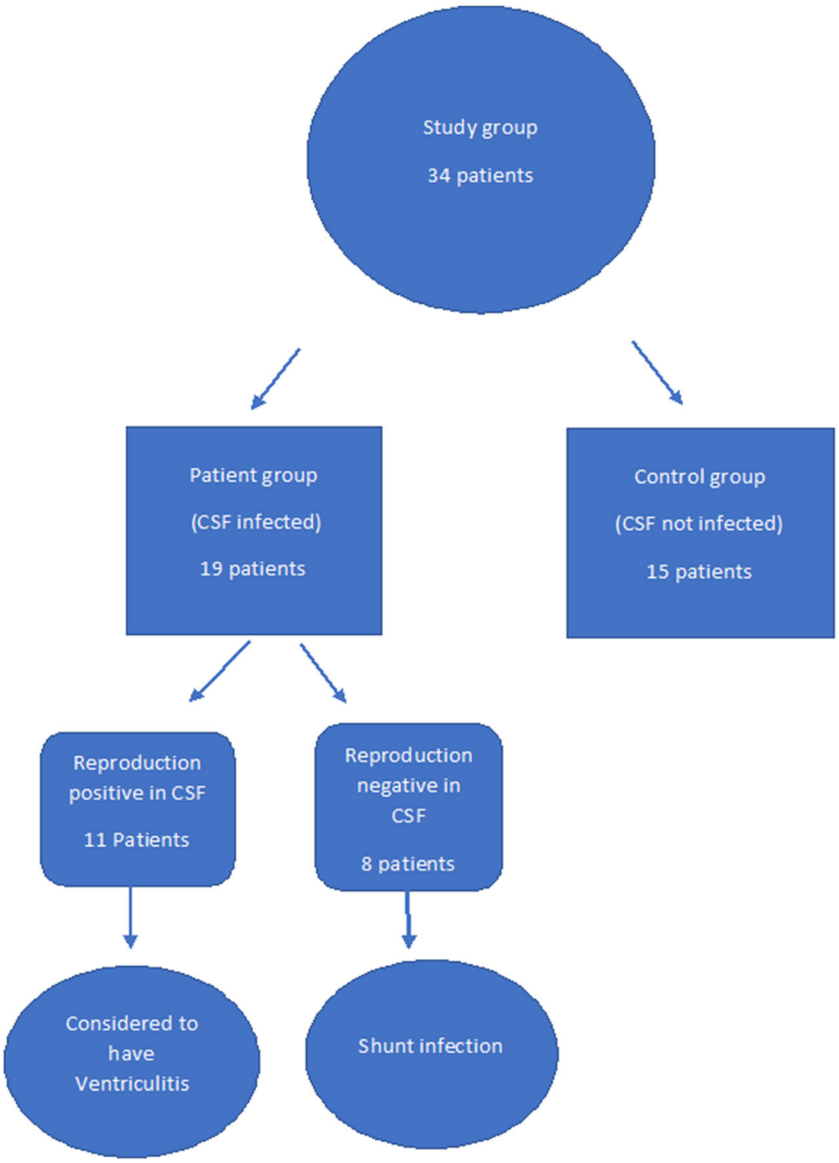


**Fig. 1** The flow diagram briefly explains the selection of the study group

## Results

In the present study, the plasma CRP, ESR, and WBC levels in the group considered to have shunt infection and/or ventriculitis were higher than those of the control group ($p < 0.001$, $p < 0.011$, $p < 0.0001$, respectively). From the CSF evaluation parameters, total protein levels were significantly higher in the patient group as expected, while the CSF glucose level was significantly lower ($p < 0.001$).

Of the patients diagnosed with VP shunt-related infection or ventriculitis, 11 patients with growth in the CSF culture and ependymal contrast enhancement on CT were considered to have ventriculitis and 8 patients with no growth in the CSF culture were considered to have shunt infection. In the CSF direct microscopic examination, the mean number of cells (100 cells/$mm^3$), IL-1β level (12 pg/ml), CRP level (1.9 mg/l), and blood leukocyte (WBC) level ($14.6*10^9$/L) of the patients with ventriculitis were significantly higher than those without growth who were diagnosed with shunt infection ($p = 0.02$, $p = 0.009$, $p = 0.004$, and $p = 0.009$, respectively) (Table 2). No significant difference was detected in the patient group considered to have reproduction in CSF between the CSF total protein, glucose, ESR, and TNF-α levels (Table 2). During the evaluation of the patients with reproduction in the CSF culture, 7 (63%) patients were observed to have *Staph epidermidis* (gr+, coagulase negative), 2 (19%) were seen to have *Klebsiella pneumonia* (gram-negative), 1 (9%) patient was seen to have *Pseudomonas aeruginosa* (gram-negative), and 1 (9%) patient was seen to have *Candida albicans* (gram-positive, diploid fungus) reproduction (Tables 3 and 4).

In the present study, we tried to determine a cutoff value for IL-1β to predict culture positivity. Sensitivity was 90.9%, and

**Table 1** Distribution of variables in the patient and control groups

| | Reproduction negative in CSF culture (−) (*n* = 8) | Reproduction positive in CSF culture (+) (*n* = 11) | Control (*n* = 15) | |
|---|---|---|---|---|
| | Med (min-max) | Med (min-max) | Med (min-max) | *p* |
| IL-1β | 3.2 (0.7–12.9) pg/ml | 12.0 (2.6–76.1) pg/ml | 0.0 (0.0–6.5) pg/ml | *0.0001* |
| TNF-α | 1.2 (0.8–1.5) pg/ml | 1.0 (0.7–1.9) pg/ml | 0.8 (0.5–1.4) pg/ml | 0.134 |
| ESR | 21 (18–40) mm/h | 28 (19–40) mm/h | 14 (4–50) mm/h | *0.011* |
| CRP | 1.1 (0.9–1.8) mg/l | 1.9 (1.0–5.2) mg/l | 0.6 (0.3–12.9) mg/l | *0.001* |
| WBC | 12,000 (2600–13,600)/mm | 14,600(10,500–24,700)/mm | 7500 (2740–12,000)/mm | *0.0001* |
| NE % | 62 (26–78) | 65 (33–80) | 61 (17–91) | 0.606 |
| LY % | 26 (11–65) | 24 (9–50) | 13(2–77) | 0.115 |
| CSF protein | 73 (49–578) mg/dl | 125 (60–1747) mg/dl | 35 (9–73) mg/dl | *0.0001* |
| CSF glucose | 39 (12–50) mg/dl | 35 (3–70) mg/dl | 64 (26–83) mg/dl | *0.0001* |
| Direct microscobic cell evaluation | 35 (20–180)/$mm^3$ | 100 (100–300)/$mm^3$ | – | *0.0001* |

Italic values are written to mention $p < 0.05$ is found to be statistically significant

*ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *CSF* cerebrospinal fluid, *WBC* white blood cell, *Med* median, *Min* minimum, *Max* maximum

specificity was 82.6% in patients with shunt infection and ventriculitis when the cutoff value for IL-1β was 4.0 pg/ml ($p = 0.0001$). The area under the ROC curve (AUC) was found to be 0.927 according to the ROC analysis result. Thus, the obtained cutoff value gives a correct result of 92.7% (Fig. 2).

## Discussion

Ventriculitis, which is known to develop after chronic inflammation and bacterial invasion of the ventricular surface with a recurrence of shunt infections, is more severe than traditional shunt infections and is highly likely to result in permanent neurological and severe cognitive sequelae [10, 24, 29]. Together with difficulty in diagnosing the disease, the long and troublesome treatment causes the clinical management to become difficult. From the results of this study, it was concluded that the IL-1β level was a very useful measurement to rapidly and effectively predict reproduction in the CSF culture received from the ventricle of patients diagnosed with ventriculitis due to reproduction positivity in the CSF culture, in accordance with guidelines, studies, and appropriate clinical and laboratory parameters.

**Table 2** Distribution of the variables according to reproduction in culture in the patient group

| | No | | Yes | | |
|---|---|---|---|---|---|
| | *n* | Med (min-max) | *n* | Med (min-max) | *p* |
| Age | 8 | 1 (0–17) | 11 | 2 (0–17) | 0.968 |
| IL-1β (pg/ml) | 8 | 3.1 (0.7–12.9) | 11 | 12 (2.6–76.1) | *0.009* |
| TNF-α (pg/ml) | 8 | 1.2 (0.8–1.5) | 11 | 1 (0.7–1.9) | 0.310 |
| ESR (mm/h) | 8 | 21.5 (18–40) | 11 | 28 (19–40) | 0.062 |
| CRP (mg/l) | 8 | 1.1 (0.9–1.8) | 11 | 1.9 (1–5.2) | *0.004* |
| WBC /$mm^3$ | 8 | 12,000 (2600–13,600) | 11 | 14,600 (10500–24,700) | *0.009* |
| NE (%) | 8 | 62 (26–78) | 11 | 65 (33–80) | 0.351 |
| LY (%) | 8 | 26 (11–65) | 11 | 24 (9–50) | 0.600 |
| CSF protein (mg/dl) | 8 | 73 (49–578) | 11 | 125 (60–1747) | 0.177 |
| CSF glucose (mg/dl) | 8 | 39 (12–50) | 11 | 35 (3–70) | 0.968 |
| Direct microscobic cell evaluation/$mm^3$ | 8 | 35 (20–180) | 11 | 100 (60–300) | *0.020* |

Italic values are written to mention $p < 0.05$ is found to be statistically significant

*ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *CSF* cerebrospinal fluid, *WBC* white blood cell, *Med* median, *Min* minimum, *Max* maximum

**Table 3** Percent distribution of microorganisms detected in culture

| | % | N |
|---|---|---|
| *Staphilococcus epidermidis* | 63% | 7 |
| *Klebsiella pneumonia* | 19% | 2 |
| *Candida albicans* | 9% | 1 |
| *Pseudomonas aeruginosa* | 9% | 1 |

Ventriculitis and meningitis associated with shunt infections require long-term medical treatment. Although different definitions for the diagnosis of ventriculitis have been reported in the literature, the most common diagnostic method is the reproduction of microorganism in CSF culture [1, 3]. The current use of acute phase reactants such as CSF leukocyte count, plasma CRP level, and procalcitonin, which are widely used as infection markers in the evaluation of systemic inflammatory response, is very limited in the diagnosis of ventriculitis. Generally, even in severe clinical settings such as shunt-related ventriculitis based on culture results taken from the shunt pump, there is not the required level of reproduction in cultures; and with the waiting time of 48–72 h to protect against the risk of contamination, they are not always useful. Therefore, the current treatment for patients with high clinical suspicion for ventriculitis is long-term intravenous and/or intraventricular empirical antibiotics.

Biochemical evaluation of CSF is essential in the diagnosis and treatment of shunt infections. For shunt infections, it is significant to have more than 100 WBC per millimeter of CSF [3]. In bacterial infections, a CSF glucose level decrease while the protein level increases, however, is not specific. In the "Infectious Diseases Society of America" (IDSA) guidelines, updated in 2017, CSF culture is still considered to be the gold standard in patients who are thought to have an infection by cell counting for the diagnosis of shunt-related ventriculitis and meningitis, but the absence of reproduction in the culture was stated to be not enough to exclude the diagnosis [32]. It has been suggested that in such cases, additional laboratory tests (such as serum and CSF procalcitonin levels and CSF beta-D glucan levels) would increase the sensitivity [18–20].

In this study, we studied proinflammatory cytokines in the CSF, direct microscopic examination of WBCs, gadolinium contrast-enhanced CT, routine CSF biochemical evaluation, and culture evaluation to immediately diagnose ventriculitis without waiting for culture results to start treatment without delay. CSF IL-1β and TNF-α levels were investigated both in the patient and control groups Table 5.

The high level of protein and low level of glucose detected in CSF were consistent with the literature. ESR and CRP in blood serum were significantly high in the patient group compared to the control group (respectively $p = 0.011$, $p = 0.001$).

TNF-α, which is known to be a critical cytokine in the inflammatory process, is also called "cachexin" and initiates inflammation. It emerges as a response within the first 6 h of inflammation, reaches peak levels within 24 h, and remains consistently high for the duration of the stimulus. TNF triggers systemic inflammation separately or in combination with IL-1 and leads to the appearance of inflammatory clinical findings (e.g., fever, loss of appetite, weight loss) [2, 22]. Increased TNF levels have been reported in patients with infectious diseases, burns, attacks of acute rheumatoid arthritis, and with transplant rejection [7, 9]. Although it mediates many physiological changes during the infection, it is not always possible to detect TNF. TNF-α and IL-1β cytokines have different release mechanisms in the presence of inflammation. Both cytokines increase in CSF infections [1, 4, 5, 11, 16, 27, 28, 30]. In a meta-

**Table 4** Cytokine level, protein, and direct microscopic evaluation results of the patient group with reproduction in culture

| | Pathogen | IL-1β (pg/ml) | TNF-α (pg/ml) | CSF protein (mg/dl) | Cell count |
|---|---|---|---|---|---|
| Sample 2 | *Staph.epidermidis* | 6.2 | 1.1 | 121 | 100 pmnl/mm$^3$ |
| Sample 6 | *Staph.epidermidis* | 59.6 | 1.0 | 200 | 100 pmnl/mm$^3$ |
| Sample 7 | *Staph.epidermidis* | 43.7 | 0.8 | 1747 | 180 pmnl/mm$^3$ |
| Sample 8 | *Staph.epidermidis* | 4.3 | 0.9 | 194 | 100 pmnl/mm$^3$ |
| Sample 9 | *Staph.epidermidis* | 76.1 | 1.2 | 90 | 300 pmnl/mm$^3$ |
| sample 12 | *Staph.epidermidis* | 8.1 | 0.7 | 115 | 100 pmnl/mm$^3$ |
| Sample 17 | *Staph.epidermidis* | 12.0 | 1.0 | 140 | 100 pmnl/mm$^3$ |
| Sample 13 | *Klebsiella pneumonia* | 9.1 | 0.8 | 60 | 100 pmnl/mm$^3$ |
| Sample 18 | *Klebsiella pneumonia* | 14.4 | 1.9 | 125 | 160 pmnl/mm$^3$ |
| Sample 11 | *Pseudomonas aeruginosa* | 14.8 | 1.0 | 143 | 100 pmnl/mm$^3$ |
| Sample 1 | *Candida albicans* | 2.6 | 1.0 | 81 | 100 pmnl/mm$^3$ |

*PMNL* polymorphonuclear leukocyte

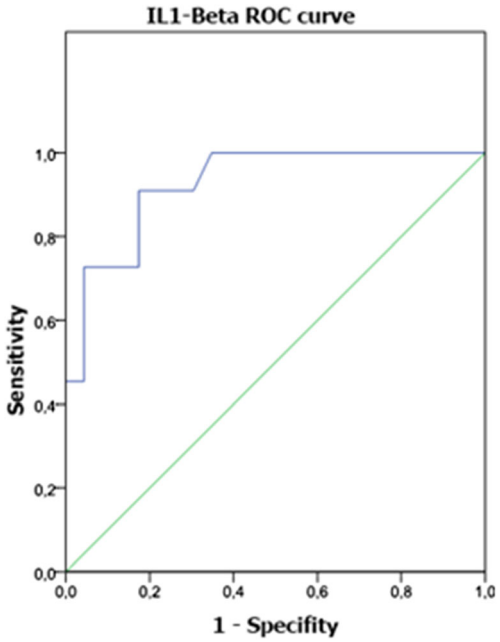


**Fig. 2** IL-1β values over 4.0 pg/ml; the probability of predicting positive culture outcome is 92.7% with 90.9% sensitivity and 82.6% specifity. IL-1β ROC curve AUC (area under curve) = 0.927; cutoff value for IL-1β is 4 pg/ml. Sensitivity, 90.9 %; Specifity, 82.6%; $p = 0.000$

analysis by Panato et al., the TNF-α and IL-1β levels were emphasized as indicators with high sensitivity for the differentiation of bacterial and aseptic meningitis diagnoses [20].

In the present study, the CSF IL-1β level was significantly high in the patient group compared to the control group ($p < 0.0001$). It was also determined that the CSF IL-1β levels of the patients diagnosed with ventriculitis due to reproduction in the CSF culture taken from within the ventricle were significantly higher than those of the patients with shunt infection without reproduction in the CSF culture ($p = 0.009$).

There are several studies in the literature reporting high levels of TNF-α in CSF infections [18, 21, 31]. In the present study, TNF-α level was higher in the patients who were considered to have ventriculitis compared to the patients of the control group; however, a significant favorable result could not be achieved.

Shunt infections, which are often slowly progressive infections, cause a headache and high fever. Therefore, a great majority of the patients use anti-inflammatory drugs prior to hospital admission. IL-1β is anti-inflammatory, steroid-based and less affected by antibiotic treatment than TNF-α, and has therefore been emphasized as a more reliable test at the time of admission [5, 10]. IL-1β is a useful parameter which can be studied by micro ELISA in 2 h. The rapidly obtainable outcome may facilitate diagnosis when CSF infection is suspected. In patients with shunt infections, intrathecal antibiotherapy can be added when ventriculitis is suspected; this may shorten the duration of intravenous antibiotherapy [6, 34]. If the diagnosis of ventriculitis can be accelerated with IL-1β, we can shorten the duration of the antibiotics given to the patient and provide enhanced patient care.

The fact that the clinical and laboratory outcome characteristics of the patients are not known can be considered limitations of the present study. There was also the possibility of the presence of patients diagnosed with ventriculitis in the patient group, for whom no active agent could be isolated in the culture, and this could also be a drawback to the study.

## Conclusion

The results of the study demonstrated that the diagnosis of ventriculitis can be facilitated with the evaluation of the CSF IL-1β level without waiting for culture result and that it would, therefore, be a very valuable laboratory test for the early diagnosis of VP shunt-related ventriculitis.

**Table 5** Distribution of cytokine values in the patient and control groups

| | | IL-1β (pg/ml) | TNF-α (pg/ml) | CSF protein (mg/dl) |
|---|---|---|---|---|
| Reproduction in CSF (−) | *N* | 8 | 8 | 8 |
| | Med (min-max) | 3.2 (0.7–12.9) | 1.2 (0.8–1.5) | 73.0 (49–578) |
| Reproduction in CSF (+) (Ventriculitis) | *N* | 11 | 11 | 11 |
| | Med (min-max) | 12.0 (2.6–76.1) | 1.0 (0.7–1.9) | 125.0 (60–1747) |
| Control group (patients with shunt disfunction) | *N* | 9 | 9 | 9 |
| | Med (min-max) | 0.0 (0.0–6.5) | 0.8 (0.5–14) | 35.0 (14–58) |
| Control group (patients with tumor) | *N* | 6 | 6 | 6 |
| | Med (min-max) | 1.8 (0.0–3.2) | 1.0 (0.7–1.3) | 34.0 (9–73) |

*CSF* cerebrospinal fluid, *Med* median, *Min* minimum, *Max* maximum

Further broad participation-controlled prospective studies are needed to study this further.

**Authors' contributions** Semih K. Olguner, Bulent Boyar, Derya Alabaz, and Tahsin Erman were involved in the study conception and design. Ali İhsan Okten, Ali Arslan, Emre Bilgin, and Kadir Oktay were responsible for the data analysis. All authors contributed to the discussion, interpreted the findings, helped write, reviewed/edited the manuscript for intellectual content, and read and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval and consent to participate** All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Çukurova Medical Faculty. All participants provided informed consent.

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