

VIEWPOINT

Use of α -Defensins to Help Diagnose Nosocomial Ventriculitis



James B. Doub*

© 2022 Springer Science+Business Media, LLC, part of Springer Nature and Neurocritical Care Society

Abstract

Ventriculitis is a severe complication of indwelling neurosurgical devices that is associated with significant morbidity and mortality. The incidence rate of ventriculitis is approximately 10% with external ventricular drains. Obstinate, patients with these indwelling neurosurgical devices are prone to have traditional cerebral spinal fluid parameters that lack sensitivity and specificity in diagnosing nosocomial ventriculitis. In addition, diagnosis can be arduous given that indolent pathogens are commonly implicated. Therefore, diagnosis is difficult but paramount to thwart the morbidity and mortality associated with this infectious condition as well as to reduce the prolonged use of broad-spectrum antibiotics. As we extrapolate from prosthetic joint infections, for which diagnosis can also be challenging, we learn that the use of α -defensins as a diagnostic biomarker for nosocomial ventriculitis may hold promise. Herein, the viewpoint of using α -defensins as a diagnostic biomarker for nosocomial ventriculitis is discussed.

Keywords: Ventriculitis, α -defensins, Central nervous system infections, Prosthetic joint infections, External ventricular drain

Ventriculitis is a severe central nervous system (CNS) condition that involves inflammation of the ependymal lining of the cerebral ventricles [1]. Common symptoms include fever, altered mental status, severe headaches, and sepsis [2]. A wide range of pathogens have been implicated, but with nosocomial ventriculitis, many indolent pathogens are implicated, thus not allowing for these pathogens to be readily cultured [2]. Treatment entails rapid identification and aggressive antimicrobial treatment to prevent long-term sequelae and reduce mortality [1, 2].

Nosocomial ventriculitis is usually associated with neurosurgical devices (external ventricular drains [EVDs] and shunts) but can also occur after neurosurgical procedures and trauma [1]. EVDs are habitually used in Intensive care units to monitor and control increased intracranial pressure in the acute setting [2].

Complications from EVDs include hemorrhage, hygromas, and infections [3]. Infections are usually secondary to microbes colonizing the device at the time of insertion, to introduction with subsequent manipulations, or to retrograde translocation of microbes [2–4]. The incidence of nosocomial ventriculitis varies widely in the reported literature, with EVD-associated ventriculitis being reported as high as 22%, but the current rate is approximately 10% [2]. Incidence is also strongly correlated with the duration of EVD residence, with longer durations being associated with increased risk of ventriculitis [2–4].

The diagnosis of CNS infections is commonly conducted with evaluation of cerebral spinal fluid (CSF) for derangements of protein, glucose, cell count, gram stain, and culture. However, in nosocomial ventriculitis, patients can have abnormal CSF parameters from underlying CNS pathologies, complicating diagnosis [5, 6]. Furthermore, pleocytosis can occur secondary to CNS hemorrhages and from chemical meningitis [2, 6]. Obstinate, patients with hemorrhages and noninfectious ventriculitis often have similar symptoms, such as fever, headache, and altered mental status [2, 6]. Consequently,

*Correspondence: Jdoub@ihv.umaryland.edu
Division of Clinical Care and Research, Institute of Human Virology,
University of Maryland School of Medicine, 725 West Lombard Street,
Baltimore, MD, USA

symptoms and traditional diagnostic CSF testing parameters (cell count, protein level, and glucose level) have significantly less specificity and sensitivity in nosocomial ventriculitis compared to community-acquired meningitis [7]. This has led to the evaluation of several additional parameters to aid in diagnosis, which include CSF lactate level, CSF microbial polymerase chain reaction testing, and procalcitonin level, but these parameters have conflicting data supporting effectiveness [2]. Therefore, novel diagnostics are needed to help clinicians diagnose nosocomial ventriculitis to thereby reduce morbidity and mortality and thwart the use of and the complications associated with broad-spectrum antibiotics. One such biomarker that holds theoretical promise in diagnosing ventriculitis is α -defensins.

Human α -defensins are small cationic peptides with 29–33 amino acids that are sequestered in neutrophil granules [8]. These peptides are innate antimicrobial molecules with broad antimicrobial activity to gram-positive and gram-negative bacteria, fungi, and enveloped viruses [8]. They are released by activated neutrophils when they are exposed to microbes to disrupt microbial membrane integrity and function [9]. Low levels of α -defensins can be present in the serum of healthy patients, but levels increase significantly in infectious conditions, causing sepsis, with high levels localized to areas where infections are present [10, 11].

Consequently, α -defensins can be a helpful diagnostic tool whereby increased levels of α -defensins in specific locations are suggestive of an underlying infectious process. This biomarker has been proven effective in periprosthetic joint infections (PJIs) in which diagnosis is important because prosthetic removal is standard care for chronic infections but is associated with significant morbidity, mortality, and financial ramifications [12]. Moreover, in PJI, classic serological and synovial fluid parameters lack sensitivity and specificity, and infections are often secondary to indolent pathogens [13, 14]. The effectiveness of α -defensins in aiding in diagnosing PJI has been proven in several clinical trials, with a meta-analysis showing pooled sensitivity and specificity of 100% and 96%, respectively [13, 14]. Therefore, the use of α -defensins has been incorporated into guidelines for prosthetic joint infection diagnosis [15] and is a commercially available diagnostic test (CD laboratories, Towson, Maryland).

Although there are robust data proving the effectiveness of this biomarker in diagnosing PJIs, there are scant data on its use and/or concentrations in the CSF with CNS infections, and no study has evaluated this biomarker in nosocomial ventriculitis. However, three studies do support the use in CNS infections. In one study, α -defensins had higher CSF concentrations in patients

with bacterial meningitis than in patients with aseptic conditions and healthy volunteers [16]. In a follow up study, the concentration of α -defensins in the CSF of pediatric patients with meningitis was shown to be significantly elevated compared with those without bacterial meningitis [17]. This study also proved that higher CSF concentrations of α -defensins had greater specificity and sensitivity than lower concentrations [17]. Lastly, in patients with West Nile neuroinvasive disease, there were higher concentrations of α -defensins present compared with patients who did not have neuroinvasive disease [18]. These studies reinforce that neutrophils in the CNS can secrete high concentrations of α -defensins in the CSF when CNS infections are present.

Overall, α -defensins hold theoretical promise in aiding in diagnosing ventriculitis. Furthermore, there are several similarities that make diagnosing PJI and ventriculitis difficult but for which α -defensins have been proven to not be affected, thereby aiding diagnosis. In PJI, α -defensins have been demonstrated to be elevated in joints, even despite the use of prolonged systemic antibiotics [13–15]. This is advantageous because conventional CSF parameters and levels of neutrophils are often altered in nosocomial ventriculitis when broad-spectrum antibiotics are used. Likewise, high levels of red blood cells can be present in the joints of patients with PJI, but this does not significantly alter the effectiveness of this biomarker, which is important because in nosocomial ventriculitis, the presence of blood in the CSF can be a common occurrence with some CNS conditions [13, 14]. Additionally, even though α -defensins have very high sensitivities and specificities for diagnosing PJI, they are correlated with conventional parameters obtained from the synovial fluid as part of standard care testing [15]. Therefore, in nosocomial ventriculitis, α -defensins can be paired with conventional CSF diagnostic parameters that are obtained as part of standard care testing.

To conduct this research, small proof-of-concept trials will first need to be run, comparing α -defensin concentrations in culture-proven nosocomial ventriculitis with concentrations from patients who do not have nosocomial ventriculitis. To reduce confounding, this would need to be piloted in patients who have EVD in situ and proven or disproven ventriculitis. This would create a foundation to support or refute the use of this biomarker, and if supported, larger studies could then be conducted to establish sensitivity and specificity of this biomarker in ventriculitis. These early studies would first need to use immunoassays, as previously discussed by others [18, 19]. Although the morbidity and mortality associated with nosocomial ventriculitis rivals that of PJIs, the research is unlikely to be chaperoned by large companies given that the financial ramifications are not as significant as

those seen in PJI [20]. Therefore, early studies will need to be piloted at a single center or small collaboration of centers and then tested more broadly before being developed into a diagnostic platform. This may be a hindrance because funding would need to be obtained, but the demand for improvements in diagnostic testing and the clinical implications associated with nosocomial ventriculitis support the need to evaluate this novel diagnostic. Without novel diagnostics, patients will continue to either be treated unnecessarily with prolonged antibiotics or have truncated antibiotic courses, thereby placing them at risk for significant morbidity and mortality.

Using this biomarker in ventriculitis does have some limitations that will need to be realized. For one, α -defensins are small cationic molecules that could potentially reach the CSF, especially in conditions such as subarachnoid hemorrhages that may disrupt the blood–brain barrier. Subsequently, establishing a cutoff to reduce the confounding serum levels of α -defensins would be needed [17, 18, 21]. As seen in PJI, which has no barrier to protect the joint from systemic α -defensin concentrations, a cutoff of 5.2 mg/L has been established. To maximize the specificity and sensitivity of this diagnostic test, a similar cutoff may be needed but would need to be validated in early ventriculitis studies [20]. Recent literature has shown that interleukin-6 levels are elevated in subarachnoid hemorrhages, as has been shown after joint arthroplasties [22, 23]. Interleukin-6 has been shown to increase the release of α -defensins in patients with COVID-19, but the impact of increased interleukin-6 levels on α -defensins levels in conditions such as subarachnoid hemorrhages is unknown [24]. Consequently, even though surgical trauma induces increased interleukin-6 production, this cytokine will likely need to be evaluated in tandem in early studies to ensure this does not confound the levels of α -defensins. Lastly, the cost of α -defensins in diagnosing PJI is expensive, costing more than 500 dollars per test, but the cost is also associated with additional tests (microbial culture, synovial fluid C-reactive protein, and other synovial fluid tests). The point-of-care lateral flow α -defensin test kit is much cheaper and even less expensive, costing well under 100 dollars per sample. As are serum α -defensin enzyme-linked immunosorbent assays, which could be tailored toward CSF samples to evaluate this biomarker as a diagnostic for ventriculitis.

In conclusion, nosocomial ventriculitis can be arduous to diagnosis in part from the limited sensitivity and specificity of traditional CSF parameters and the indolent nature of the causative pathogens. However, the incidence and clinical ramifications of this severe infectious condition should drive research in evaluating α -defensins as a diagnostic biomarker, especially given that this

biomarker has been used in a similar fashion with PJIs. As outlined here, α -defensins may hold promise in diagnosing nosocomial ventriculitis, thereby improving morbidity and mortality and reducing the unnecessary use of broad-spectrum antibiotics.

Source of Support

None.

Conflicts of interest

The author has no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 12 August 2022 Accepted: 8 November 2022

Published: 30 November 2022

References

1. Hasbun R. Healthcare-associated ventriculitis: current and emerging diagnostic and treatment strategies. *Expert Rev Anti Infect Ther*. 2021;19(8):993–9.
2. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64(6):e34–65.
3. Bischoff P, Schröder C, Gastmeier P, Geffers C. Surveillance of external ventricular drainage-associated meningitis and ventriculitis in German intensive care units. *Infect Control Hosp Epidemiol*. 2020;41(4):452–7. <https://doi.org/10.1017/ice.2019.367>.
4. Ramanan M, Lipman J, Shorr A, Shankar A. A meta-analysis of ventriculostomy-associated cerebrospinal fluid infections. *BMC Infect Dis*. 2015;15:3.
5. Conen A, Walti LN, Merlo A, Fluckiger U, Battagay M, Trampuz A. Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. *Clin Infect Dis*. 2008;47(1):73–82.
6. Forgacs P, Geyer CA, Freidberg SR. Characterization of chemical meningitis after neurological surgery. *Clin Infect Dis*. 2001;32(2):179–85.
7. Schade RP, Schinkel J, Roelandse FW, et al. Lack of value of routine analysis of cerebrospinal fluid for prediction and diagnosis of external drainage-related bacterial meningitis. *J Neurosurg*. 2007;106(5):941.
8. Selsted ME, White SH, Wimley WC. Structure, function, and membrane integration of defensins. *Curr Opin Struct Biol*. 1995;5(4):521–7.
9. Ganz T. Defensins: antimicrobial peptides of innate immunity. *Nat Rev Immunol*. 2003;3:710–20.
10. Zhang H, Porro G, Orzech N, Mullen B, Liu M, Slutsky AS. Neutrophil defensins mediate acute inflammatory response and lung function in a dose-dependent fashion. *Am J Physiol Lung Cell Mol Physiol*. 2001;280:L947–54.
11. Panyutich AV, Panyutich EA, Krapivin VA, Baturevich EA, Ganz T. Plasma defensin concentrations are elevated in patients with sepsis or bacterial meningitis. *J Lab Clin Med*. 1993;122:202–7.
12. Natsuhara KM, Shelton TJ, Meehan JP, Lum ZC. Mortality during total hip periprosthetic joint infection. *J Arthroplasty*. 2019;34(7S):S337–42.
13. Deirmengian CA, et al. Combined measurement of synovial fluid α -defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. *JBJS Am*. 2014;96(17):1439–45.
14. Wyatt MC, Beswick AD, Kunutsor SK, Wilson MJ, Whitehouse MR, Blom AW. The alpha-defensin immunoassay and leukocyte esterase colorimetric strip test for the diagnosis of periprosthetic infection: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2016;98(12):992–1000. <https://doi.org/10.2106/JBJS.15.01142>.

15. Parvizi J, Tan TL, Goswami K, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. *J Arthroplasty*. 2018;33(5):1309-1314.e2.
16. Ihi T, Nakazato M, Mukae H, Matsukura S. Elevated concentrations of human neutrophil peptides in plasma, blood, and body fluids in patients with infections. *Clin Infect Dis*. 1997;25:1134-40.
17. Maffei FA, Heine RP, Whalen MJ, Mortimer LF, Carcillo JA. Levels of antimicrobial molecules defensin and lactoferrin are elevated in the cerebrospinal fluid of children with meningitis. *Pediatrics*. 1999;103(5 Pt 1):987-92.
18. Fraiser C, Papa A, Granjeaud S, et al. Cerebrospinal fluid biomarker candidates associated with human WNV neuroinvasive disease. *Plos One*. 2014;9(4):93637.
19. Premkumar A, Kolin DA, Farley KX, et al. Projected economic burden of periprosthetic joint infection of the hip and knee in the United States. *J Arthroplasty*. 2021;36(5):1484-1489.e3.
20. Bonanzinga T, Ferrari MC, Tanzi G, Vandenbulcke F, Zahar A, Marcacci M. The role of alpha defensin in prosthetic joint infection (PJI) diagnosis: a literature review. *EFORT Open Rev*. 2019;4(1):10-3. <https://doi.org/10.1302/2058-5241.4.180029>.
21. Payutich AV, Voitenok NN, Lehrer RI, Ganz T. An enzyme immunoassay for human defensins. *J Immunol Methods*. 1991;141:149-55.
22. Barker T, Henriksen VT, Rogers VE, Trawick RH, Momberger NG, Lynn RG. Multi-vitamin supplementation blunts the circulating IL-6/IL-10 ratio increase after knee arthroplasty: a randomized, double-blind, placebo controlled study. *Cytokine*. 2021;140:155435.
23. Simon M, Grote A. Interleukin 6 and aneurysmal subarachnoid hemorrhage a narrative review. *Int J Mol Sci*. 2021;22(8):4133. <https://doi.org/10.3390/ijms22084133>.
24. Abdeen S, Bdeir K, Abu-Fanne R, et al. Alpha-defensins: risk factor for thrombosis in COVID-19 infection. *Br J Haematol*. 2021;194(1):44-52. <https://doi.org/10.1111/bjh.17503>.