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Case Report

Absence of immunoreaction and cellular adhesion in a polyvinylpyrrolidone-coated ventricular catheter with choroid plexus obstruction: A case report

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ABSTRACT

Background: While a variety of modalities are available for the treatment of hydrocephalus, ventriculoperitoneal shunting (VPS) remains the most utilized treatment. Although efficacious, VPS is susceptible to malfunction, with catheter obstruction as the primary cause of failure in pediatric patients. Prior studies have speculated that implanted catheters trigger an immune response from the central nervous system, resulting in cellular reactivity and subsequent obstruction of the device. These cells are derived from the choroid plexus (ChP), which plays an active role in immunological surveillance. Its cellular components contain some of the putative cells that contribute to ventricular catheter occlusion.

Case Description: The case illustrated herein is a patient with a functionally obstructed polyvinylpyrrolidone (PVP)-coated catheter, with ChP occluding the catheter fenestrations. While silicone catheter obstruction typically presents with fibrosis and microglial reaction, the illustrated case demonstrates the absence of an immunological response. PVP-coated catheters appear to deter cellular attachment which may dampen the immune response to the catheter in the brain. However, the case discussed postulates that ChP can still obstruct PVP-coated catheters through growth and expansion into the catheter holes and lumen, even without an immune response.

Conclusion: This case report highlights the complexity of novel catheter designs constructed from nonimmunogenic materials while considering catheter hole configuration and size to deter ChP growth into the catheter holes and the lumen to prevent cellular catheter occlusion.

Keywords: BioGlide, Choroid plexus, Hydrocephalus, Immunoreactivity, Polyvinylpyrrolidone, Ventricular catheter obstruction

INTRODUCTION

Hydrocephalus is one of the leading causes of morbidity and mortality in infants, with ventricular shunting serving as the primary treatment.[27] Unfortunately, cerebrospinal fluid (CSF) shunts have high rates of failure, with many requiring replacements or revisions. Previous studies have reported that at least 30% of shunts will fail within a year of placement,[20,23] and more than 85%

will fail within 15 years.[25] Obstruction of ventricular catheters from tissue infiltration and cellular adhesion is considered the leading cause of shunt failure in pediatric patients.[6,7] Similar analyses of infiltrative tissue have not clearly elucidated whether the tissue is infiltrative solely into the wall or lumen of the catheter. Either way, over-drainage and siphoning effects have been hypothesized as stimulants to promote tissue ingress.[15,19] Despite an improved understanding of catheter-microenvironment interactions, a definitive technique to prevent catheter occlusion has yet to be achieved.

Many studies have sought to understand the biological basis of tissue infiltration and subsequent catheter obstruction. In 1981, Go *et al*. were one of the first groups to evaluate explanted, occluded catheters histologically. Their study found cellular detritus within the catheter as early as 1-month postimplantation.[7] More recently, Hariharan *et al*. categorized the various tissues associated with ventricular catheter obstruction and found that the most common causes of obstruction were lymphocytic inflammation (29%), choroid plexus (ChP) (24%), vascularized glial tissue (24%), and foreign body giant cell reactions (5%).[11] The initiation of cellular mechanisms that underlie these obstructive processes is not fully understood. A catheter-induced immune response cascade has been proposed to play a fundamental role in device failure.[12] The immune response is thought to be driven primarily by glial activation of microglia and astrocytes, with subsequent deposition of fibrinogen and collagen in and around the catheter lumen. Given its role in immune response, ChP may also be responsible for immunological activation related to catheter obstruction through the recruitment of macrophages, as well as the production of extracellular matrix proteins associated with catheter obstruction.[11,22]

Given that ventricular catheters are susceptible to occlusion, researchers and engineers have sought to create occlusion-proof catheters. One prominent innovation is the use of polyvinylpyrrolidone (PVP), commonly known as BioGlide®, as a coating on ventricular catheters. PVP was initially created as a hydrophilic coating aimed at decreasing shunt failure by limiting bacterial colonization.[2,29] While PVP's ability to limit bacterial colonization has been demonstrated, its potential for its ability to mitigate cellular immunoreactivity has not been thoroughly researched. Herein, we present a case with catheter occlusion resulting from gross ChP obstruction in the absence of an immunologic response to the PVP-coated ventricular catheter.

CASE DESCRIPTION

The patient had a history of hydrocephalus secondary to Dandy-Walker malformation with a ventricular shunt subsequently placed at 8 months of age. The patient presented 8 years after their initial shunt placement with symptoms of shunt failure. The shunt was tapped percutaneously through needle aspiration, with no return of CSF. Imaging taken at the time of presentation demonstrated ventricular dilation compared with the baseline diminutive ventricular caliber [Figure 1].

During shunt exploration, there was no CSF flow from the PVP-coated ventricular catheter, and the proximal catheter was adherent within the ventricle. A pen-type endoscope was passed through the internal lumen of the ventricular catheter and internal debris was detached from its anchor point, freeing the catheter without removing the debris that was attached to it [Figure 2]. A new ventricular catheter was placed endoscopically away from the debris and ChP, and appropriate CSF egress was re-established.

Pathologic findings and experimentation

The explanted PVP-coated ventricular catheter was analyzed in an experimental *in vitro* model, characterizing cellular

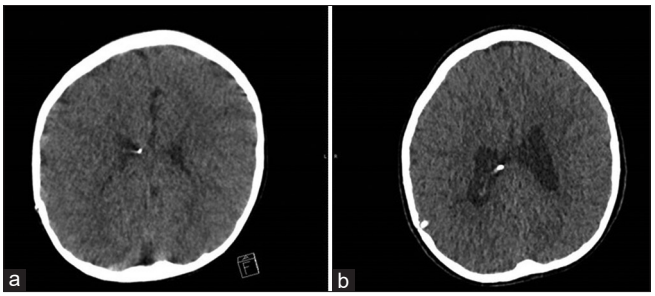

Figure 1: Comparison of computed tomography (CT) imaging. (a) baseline CT scan demonstrating baseline ventricular caliber. (b) CT scan at time of presentation with ventricular dilation.

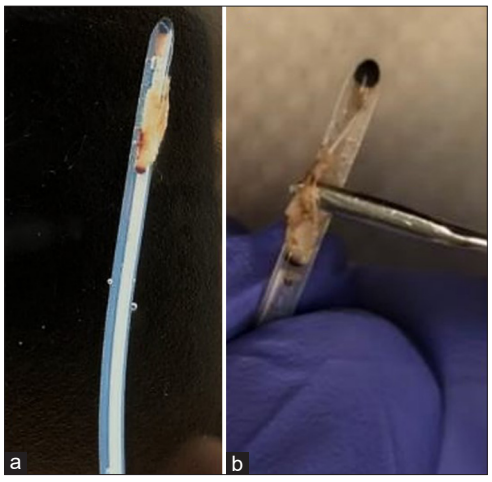

Figure 2: Polyvinylpyrrolidone (PVP)-coated obstructed catheter: (a) Obstructed PVP-coated catheter with tissue ingrowth resembling choroid plexus (ChP). (b) Image showing ingress from the ChP on the PVP-coated catheter without cellular attachment.

occlusion and hydrodynamic properties by utilizing pressure and flow rate measurements. CSF flow through the catheter was conducted with a ventricular phantom model, syringe pump (Fusion 200-X, Chemyx Inc®), pressure sensor (px409-100GUSBH, Omega®), and flow rate sensor (SLF3S-0600F, Sensirion®) as previously reported.[16] The explanted catheter was attached to a ventricular phantom model fabricated from a 3-D printer (Form 3B, Formlabs®) using medical grade flexible resin (Elastic 50A, Formlabs®). A syringe pump injected artificial CSF (Ecocyte Bioscience, #LRE-S-LSG-1000-2) into the phantom at a flow rate of 330 µl/min. Flow through the catheter was maintained at a steady rate, but higher pressures were required to overcome the tissue obstruction. These hydraulic characteristics were replicated in a control catheter (Barium Impregnated catheter, Medtronic®) with cellular obstruction [Figure 3]. Histological analysis of the catheters confirmed differing mechanisms of obstruction. The control catheter tissue demonstrated high fibrinogen levels in the catheter/cellular junction area, with macrophages present internally, while the adherent tissue in the PVP-coated catheter did not demonstrate any fibrinogen deposition or microglial activity [Figure 4].

Analyses revealed that ChP had grown into the catheter holes and attached itself to the contralateral ChP in the lumen of the catheter [Figures 2 and 4]. These observations provide evidence that the PVP-coated catheter surface did not elicit an immune response. This conclusion is further supported by the *in vitro* testing and histopathological image analysis shown in Figure 4.

DISCUSSION

There is an extensive history of shunt catheter surface modifications to mitigate shunt failure. Nulsen and Spitz introduced the first indwelling ventricular shunt system using rubberized catheters.[18] Rubberized catheters were utilized until Ingraham suggested the use of polyethylene (PE) in 1947.[14] Unfortunately, PE catheters had many complications, prompting the popularization of silicone catheters in the 1950s. Further advancements were made in the 1980s, with the introduction of antibiotic-impregnated catheters to prevent occlusion associated with microorganism colonization.[1,9]

In 1992, Gower *et al.* utilized expanded polytetrafluoroethylene (ePTFE) as a novel shunt catheter material.[9] Commonly known as Gore-Tex, this material was found to be safe for cerebral implantation, but the interactions of cells within the surface of the catheters rendered ePTFE a poor candidate to replace silicone elastomer in cerebral shunt devices. Modern devices, such as PVP-coated silicone catheters, represent an attempt to create a hydrophilic surface designed to decrease bacterial colonization.[2,29] Contardi *et al.* applied PVP with hyaluronic acid as a bilayer to confirm biocompatibility with *in vivo* and *in vitro* models, promoting an anti-inflammatory response.[5] It remains unclear whether PVP directly promotes an anti-inflammatory reaction, or there is an existing indirect effect of the antiseptic against bacterial toxins.

At present, histological research specific to explanted PVP-coated ventricular catheters is limited. Other studies with respect to failed shunts draw a parallel to the current findings. Sarkiss *et al.* conducted a histological analysis of 85 explanted catheters examining characteristics of occluded shunts as a function of time to revision.[21] Results from the study elucidated that a longer duration of shunt implantation was associated with an inverse relationship to inflammatory infiltrates, characterized by the presence of lymphocytes, macrophages, and microglial cells. Shunt implantation >3 years was associated with a greater likelihood of reactive infiltration, characterized by fibro-connective tissue, reactive astrocytes, and sporadic Rosenthal fibers in a nononcologic

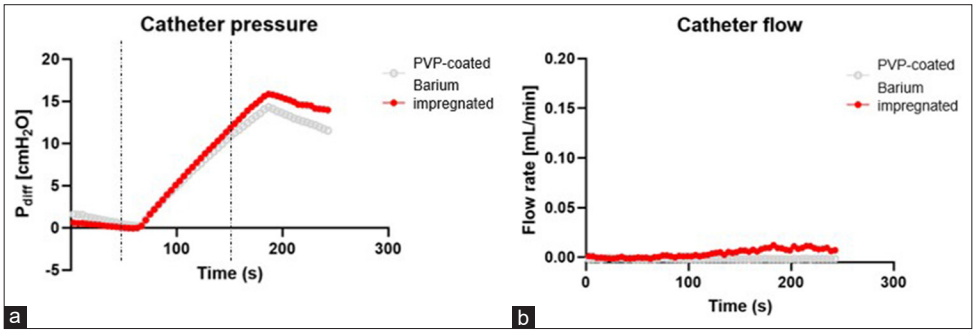

Figure 3: Comparison of polyvinylpyrrolidone (PVP)-coated versus barium-impregnated obstructed catheter pressure and flow analysis. (a) Intracranial pressure-like graphic representation of the proximal catheters tested (PVP-coated vs. barium impregnated). Both catheters indicate malfunction as the intracranial-like pressure continued increasing while the pump was in space between dashed lines. (b) Graphic representation of catheter flow. No flow was found in either catheter, indicating total obstruction.

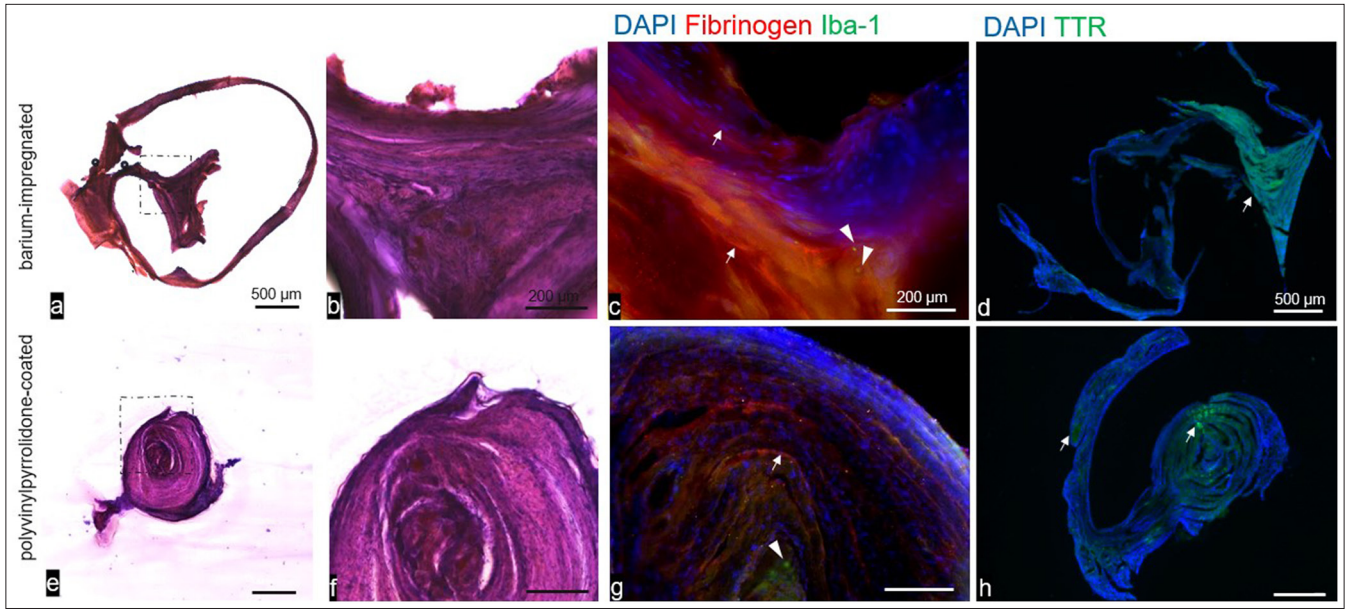

Figure 4: Histological analysis of polyvinylpyrrolidone (PVP)-coated versus barium-impregnated obstructed catheters. (a) Histological preparation stained with hematoxylin and eosin (H&E) of a transverse slice of a barium-impregnated partially obstructed catheter (Magnification: 4x). (b) Magnification (10x) of the square in a, highlighting partial obstruction by a fibrinogen layer. (c) Immunofluorescence against 4′,6-diamidino-2-phenylindole (DAPI, nuclear counterstain), fibrinogen, and Iba-1 (macrophage marker) in a parallel slice from b. The image shows high fibrinogen levels associated with the choroid plexus (ChP) (arrows) and, internally, the presence of macrophages (arrowhead). (d) Immunohistochemistry against transthyretin (TTR, choroid plexus marker) confirmed that ChP obstructed the catheter (arrow). (e-h) Histological preparations from an obstructed PVP-coated catheter with ChP similarly as in a-d. The images do not show a fibrinogen layer, as seen in the barium-impregnated catheter. Instead, low expression can be seen internally as part of the connective tissue (arrow). (h) Immunohistochemistry against TTR confirmed that ChP obstructed the polyvinylpyrrolidone-coated catheter (arrow). Arrowhead indicates few macrophages. Scale bars: a, d, e, and h; 500 µm; b, c, f, and g; 200 µm.

setting. This stands in contrast to the PVP-coated catheter removed from our patient, which had been implanted for >7 years and demonstrated occlusion with histologically normal ChP and typical connective tissue components [Figures 2-4].

Hariharan *et al.* conducted a large histological analysis of explanted ventricular catheters, reporting histological findings on 44 devices.[11] Subcategories of catheter material were not reported, but they did note that every catheter that underwent analysis showed some degree of inflammation. The results of the PVP-coated catheter studied herein, and its absence of inflammation, are thus notable.[11-13] This further supports the possibility that PVP coating on the ventricular catheter hinders the CNS immunological response of the catheter to a foreign body. Future investigation into the efficacy of PVP-coated catheters and the initiation of an inflammatory response may prompt focused applications of this material to minimize complications related to inflammatory occlusion.

ChP has been found to play an emerging role in the previously described immune response. It is located in the ventricles of the brain and is highly vascularized tissue comprised of modified ependymal cells surrounding a central stroma and vasculature, responsible for the production of CSF and clearing of waste.[3,4,8,26] It has also been associated with immunological surveillance of the central nervous system (CNS), including stimulation of inflammatory responses, initiation of immune signaling, and facilitation of T-cell proliferation.[28] As a result, ChP may be responsible for immunological activity related to catheter obstruction through the recruitment and activation of macrophages, as well as the production of extracellular matrix proteins associated with catheter obstruction.[11-13]

In this case, we postulate that the lower distal pressure in the shunt system (i.e., siphoning) promoted the "pull" of ChP into the catheter. While the gross appearance of an occluded silicone catheter would be similar, our histopathological studies demonstrated a different mechanism of occlusion: ingrowth without cellular attachment in PVP-coated catheters and cellular attachment with ingrowth on the catheter walls and into the lumen in non-PVP-coated catheters. For future catheter design considerations, the modification of the catheter hole angle and irregularity of hole placement may aid in the prevention of the ingrowth of ChP into the catheter lumen.[10,12,15,19] Catheter surface modification, such as zwitterionic polymers to reduce cell adhesion, is a possible method to prevent occlusion when cellular attachment to the catheter surface is observed.[17,24]

A novel catheter design to incorporate these modifications may be beneficial in understanding the CNS immunological response leading to silicone catheter occlusion. We propose that future designs should consider PVP-coated material and its potential to mitigate the initiation of an inflammatory response to the catheter surface.

This study is a single case report of one patient involving mechanisms of PVP-coated ventricular catheter obstruction and findings cannot be generalized for broader populations. However, these findings may promote potential new hypotheses and methodologies to be formed involving this field of research.

CONCLUSION

This case demonstrated the lack of immunoreactivity in a PVP-coated ventricular catheter. Considering previous studies of explanted shunt catheters, this finding adds to the ongoing evaluation of ventricular catheter coating materials.

While there are still significant obstacles when designing the optimal ventricular shunt catheter, this case report adds promising evidence to encourage catheter surface modification in future designs to mitigate a foreign-body immunological response and subsequent failure impacting patients.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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