Effect of shunt catheter on the systemic immune response: evaluation of neutrophil count, function, and rate of chemotaxis

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Object. The localized impairment of the host defense mechanism due to the presence of a shunt apparatus has been suggested as a risk factor for shunt infection. The purpose of this study was to evaluate the probable systemic effect of a shunt catheter on neutrophil phagocytosis and chemotaxis in vivo.

Methods. Twenty-four children with hydrocephalus who were referred to the Children’s Hospital Medical Center in Tehran for ventriculoperitoneal shunt placement were included in this study. Neutrophil count, chemotaxis, and nitroblue tetrazolium (NBT) tests were performed before and 2 months after the operation. In comparing the preoperative neutrophil count, NBT percentage, and chemotaxis (with and without the addition of a chemoattractant factor) with these same factors postoperatively, the authors found no statistically significant differences. In four children, shunt infections developed during the follow-up period. There were no significant differences between the aforementioned parameters in children with infected shunts and those with uninfected shunts.

Conclusions. The results of this study do not support the idea of systemic impairment of neutrophils after shunt insertion. Further studies with more specific methods are required to elaborate on this issue.

Key Words • hydrocephalus • shunt infection • neutrophil • chemotaxis • nitroblue tetrazolium • pediatric neurosurgery

Hydrocephalus is defined as a hydrodynamic disorder of the cerebrospinal fluid leading to a volume increase in the central nervous system.16 The development of implantable shunt devices was indeed a major advancement in the treatment of this pathological condition,17 which is associated with a high rate of mortality and morbidity if left untreated.

Shunt complications are numerous, and infection is reported to occur in 1.5 to 38% of patients with implanted devices. Despite the data available on the pathogenesis of shunt infection, few risk factors have been clearly identified. Recognition of the factors responsible for shunt infection may change the current prophylactic measures and lead to more effective treatment. Proposed risk factors include the relative immaturity of the immune system and the vulnerability of thin skin in young children,1,6,14 lengthening of the duration of the operation, the presence of cerebrospinal fluid leakage, associated spinal dysraphism, and the surgeon’s level of experience.16

Shunt infections resemble other biomaterial-associated infections and tend to be refractory to antibiotic treatment, which often necessitates removal of the device to clear the infection.3,10 The proposed reasons for this treatment failure include bacterial virulence, the properties of specific biomaterials that increase microbial adherence or alter inflammatory responses, and a preexisting impairment of the host defense mechanisms even in the absence of microbial colonization.10

Localized host defense impairment in the presence of a shunt apparatus has been suggested previously. The authors of some in vitro studies have shown that human neutrophils and monocytes do not adhere well to shunt catheters locally and are unable to phagocytose bacterial inocula present on the surface of the catheter.1 However, to our knowledge, in no in vivo study has the relationship between the shunt catheter itself and the systemic impairment of neutrophil functions been assessed.

To evaluate the probable systemic effects of the shunt catheter on neutrophil phagocytosis and chemotaxis, we conducted a before-and-after study in children who underwent shunt placement for hydrocephalus. Our main objective was to evaluate the shunt’s effect on certain aspects of the immune system and hence to suggest proper prophylactic measures.

Abbreviation used in this paper: NBT = nitroblue tetrazolium.
Clinical Material and Methods

We designed a before-and-after study with simple non-randomized sampling. Twenty-four children were selected from patients with hydrocephalus who were referred to the Children’s Hospital Medical Center in Tehran for ventriculoperitoneal shunt insertion between March 2004 and March 2005. Patients ranging in age from 1 month to 12 years were included in our study. The exclusion criteria included signs of immunodeficiency found in the medical history or during the physical examination, and the occurrence of a shunt malfunction during the follow-up period.

Each patient’s sex and age, the cause of the hydrocephalus, the incidence of meningitis during the study, and comorbidities were recorded. Written informed consent was obtained from each child’s parents, and all patients were able to withdraw from the study without constraint. Neutrophil count, chemotaxis, and NBT studies were performed both before and 2 months after the operation. The 2-month period following the operation is considered the peak time for shunt infection.

The number of neutrophils was determined by manual counting with the aid of light microscopy; absolute counts less than 1500 cells/mm³ were considered evidence of neutropenia. The NBT test was performed using the slide test method. A percentage of 90 or more was defined as normal. A chemotaxis study was performed both with and without chemoattractant factor using the Boyden chamber method. The normal values for these tests were 77 to 125 μm/second with chemoattractant factor, and 22 to 54 μm/second without chemoattractant factor.

The Fuji shunt system (MDM, Kaneka) was used in all patients and placed by the same neurosurgeon assisted by the same operating room staff, and was the first procedure performed each day. The same prophylactic antibiotic medication (cephalothin 50 mg/kg) was administered at the time anesthesia was induced, and each patient also received two doses after the operation.

All patients were followed up regarding postoperative complications in an outpatient clinic for 6 months. The protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. Statistical analysis was performed using SPSS software (version 11.5, SPSS, Inc.) using different statistical tests such as the paired t-test, analysis of variance, and McNemar test.

Results

Thirty patients fulfilled the inclusion criteria, among whom two died during the follow-up period because of underlying problems. Another was excluded from the study because of a low preoperative NBT score, and three were excluded because they were lost to follow up. Twenty-four patients completed the study (10 girls and 14 boys with a median age of 7.5 months). The most common causes of hydrocephalus in order of decreasing frequency were meningomyelocoele (33.3%), aqueductal stenosis (25%), and meningitis (12.5%).

The laboratory data are summarized in Table 1. A comparison of the mean neutrophil count before and after surgery, made with the paired t-test, showed no significant statistical difference (p = 0.5). Six patients (25%) had neutropenia before shunt insertion, and only two patients had neutropenia both before and after the surgery. There was no significant correlation between having neutropenia before and after surgery and the occurrence of infection (p = 0.3, McNemar test). Comparison of the mean NBT percentage before and after the procedure demonstrated no statistical significance (p = 0.51).

The mean rate of chemotaxis with chemoattractant factor before the operation was evaluated and showed no significant difference after the operation. In six patients, the neutrophils had impaired chemotaxis with chemoattractant factor before the surgery; in only three patients was neutrophil chemotaxis with chemoattractant factor impaired both pre- and postoperatively. No significant correlation was found after an analysis was performed using the McNemar test. Furthermore, in comparing the mean chemotaxis values without chemoattractant factor before the operation with that afterward, we found no statistically significant difference.

Considering the age of patients and the incidence of meningitis as independent variables in a multiple linear regression analysis, we found that none of these variables had a significant influence on chemotaxis with and/or without chemoattractant factor before and after surgery. The analysis of variance showed that no correlation existed between the causes of hydrocephalus and the rate of chemotaxis with or without chemoattractant factor.

Meningitis developed in four patients during the follow-up period. The mean neutrophil count in these patients was 1640 cells/mm³ preoperatively and 3052 cells/mm³ postoperatively, with a mean NBT score of 98% both before and 2 months after the operation. The mean chemotaxis measurements with chemoattractant factor before and after the procedure were 84.5 and 75.5 μm/second, respectively. The mean chemotaxis rates without factor were 54.5 μm/second before and 47.25 μm/second after shunt catheter insertion. Comparison of the neutrophil count, NBT score, and chemotaxis rate before and after the operation in patients with and without meningitis revealed no statistical significance according to an independent t-test (p > 0.05).

Discussion

Infection is a common complication tainting the considerable success in treating hydrocephalus that has been achieved with shunt placement. Prevention of shunt infection has been a major concern for all physicians involved in the management of hydrocephalus. Many factors possibly contribute to shunt infection, such as bacterial virulence fea-
tures, biomaterial properties, and host defense mechanisms; in this study we have focused on the last factor. However, uncertainties exist regarding the pathophysiological aspects of these infections and the possible role of the shunt itself in impairment of host defense mechanism. Some components of the host defense actions are assumed to change after insertion of biomaterials. Among these components, neutrophil chemotaxis and the cells’ ability to recognize, attack, and phagocytose the bacteria seem to have key functions. Neutrophils have considerable cytotoxic potential and play a role in many kinds of inflammatory reactions via the production of oxidative free radicals and cytotoxic granule constituents.\(^7\)\(^1\)\(^0\)

During the procedure for insertion of a ventricular catheter, brain cells are destroyed and blood vessels are disrupted. The immediate results are focal hemorrhage and edema that spreads into surrounding tissues. This initial trauma could be of some importance to the long-term outcome of the shunt.\(^7\) Hours to days after shunt placement, neutrophils and macrophages accumulate in a manner similar to that observed after a simple stab injury to the brain.\(^7\) Furthermore, results of previous in vitro studies have shown that the neutrophils that arise in response to biomaterials are prematurely activated by contact with the materials themselves. Shortly thereafter the cells lose their capacity to become activated in response to subsequent normal stimuli.\(^7\)\(^11\)\(^12\)\(^18\) The presence of a shunt catheter could possibly diminish the cells’ cytotoxic ability, but the extent of this impairment is questionable.

In fact, an implanted shunt catheter might have paradoxical effects: it induces the accumulation of phagocytes and at the same time can become the nidus of an intractable bacterial infection. Some authors have suggested that the greater ability of a foreign body to induce neutrophilic infiltration is related to further susceptibility to infection.\(^7\) Authors of previous studies have indicated that polymorphonuclear cells often become activated at the surface of biomaterials. These cells can release chemoattractant substances, which would serve to attract fresh polymorphonuclear cells to the surface. Kaplan and colleagues\(^9\)\(^10\) have suggested that, in addition to activation of the initial wave of neutrophils at the surface of the biomaterial, subsequent waves of neutrophils also exhibit impaired function. These authors also explained that the proinflammatory effects were limited to cells in physical contact with the implant. It is not yet clear whether this local effect exists systemically or not.

Borges\(^1\) studied the ability of human neutrophils and monocytes to adhere to shunt catheters and phagocytose bacteria in vitro. He found that the neutrophils and monocytes were unable to ingest the bacterial inoculum, and this failure seemed primarily related to the inability of white blood cells to adhere effectively to the surface of the catheters. Despite the demonstrated difficulty with adherence and migration, the neutrophils and monocytes that were able to adhere to the surface demonstrated a qualitatively normal ability to phagocytose. In contrast to Borges’ findings, Indorf et al.\(^5\) showed that the chemotaxis rate of polymorphonuclear cells on the catheter surface is diminished and proposed that the shunt apparatus itself might reduce the effectiveness of the host defense mechanism at the site of implantation.

Based on a review of the literature it is clear that controversy remains regarding the effect of the shunt apparatus on the patient’s immune defenses. In the present study, we evaluated the effect of the shunt catheter on neutrophil counts and functions such as chemotaxis rates and the intracellular killing of bacteria. Our results reveal that the insertion of a shunt does not have any significant effect on the cell count or the ability of the circulating neutrophils to function.

With regard to neutrophil cytotoxicity, we did not observe any significant difference in the NBT level before and after shunt insertion. Moreover, we did not observe any significant change in the neutrophil count before and 2 months after shunt insertion. This finding suggests again that shunt catheter insertion does not significantly impair the cellular host defense system, although previous in vitro studies have established that neutrophils at the site of catheter insertion show reduced cytotoxicity levels.\(^3\)\(^9\)\(^10\) In addition, we did not find any difference in neutrophil chemotaxis rates with or without chemoattractant factor either before or after the operation. Our findings suggest that insertion of a shunt catheter may not interfere with bloodstream neutrophil chemotaxis rates.

**Conclusions**

It is obvious that the insertion of a foreign body such as a shunt catheter realistically increases the risk of infection, but the exact basis of this process remains ambiguous. Our results do not support the hypothesis of systemic impairment of neutrophils after the insertion of a shunt. Further studies involving more specific experimental methods are required to explore this issue. Such studies will need a larger sample size so that sufficient statistical power can be obtained.

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**References**

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