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Interpretation of Cerebrospinal Fluid Parameters in Children with Hydrocephalus

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1. Introduction

Cerebrospinal fluid (CSF) is an ultrafiltrate of plasma formed by active, ATP-dependent pumps located predominantly in the choroidal epithelium. CSF is continuously produced and absorbed, turning over approximately 3-4 times per day. CSF normally is colorless, odorless, and contains very few cells. Compared to serum, CSF is low in protein, glucose, potassium and calcium, but high in sodium, magnesium, and chloride. (Burt 1993) Reference values for “normal” CSF levels are shown in Table 1.

CSF may be collected through a spinal puncture, ventricular access device or drain, or from a shunt “tap” in evaluating a child for shunt failure or infection. This chapter addresses some basic scenarios where interpretation of the CSF sample may guide clinical decision-making.

<table>
<thead>
<tr>
<th>Cerebrospinal Fluid Parameter:</th>
<th>Value:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>&lt; 4/mL</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>60-70%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>30-50%</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>0%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0%</td>
</tr>
<tr>
<td>Red Blood Cells</td>
<td>0</td>
</tr>
<tr>
<td>Protein</td>
<td>20-50 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>40-70 mg/dL</td>
</tr>
</tbody>
</table>

Table 1. Normal Cerebrospinal Fluid values in adults

2. CSF cell counts in children with shunts

Children may have different CSF counts compared to adults. For example, healthy neonates may have leukocytes in the CSF in the absence of infection or neuropathology. (Smith, Garges et al. 2008) Portnoy and Olson evaluated the CSF from 371 children who were proven to not have CNS infection or pathology (seizures). They found 1-3 WBC in 25% of all children and 1-10 WBC in 5% of normal neonates. (Portnoy and Olson 1985) Ahmed et al. found a mean of 7.3 WBC/mm³ in non-infected neonates, with a range of 0 –
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130/mm$^3$.(Ahmed, Hickey et al. 1996) (Shah, Shofer et al. 2005) Other authors have noted a wide variability of CSF cell counts in children with or without infection.(Garges, Moody et al. 2006)

The presence of a shunt may alter the chemistry and cell levels. Lenfestey et al. examined the CSF cell levels for 181 neonates with either a VP shunt or CSF reservoir and compared them to a group of neonates without ventricular catheters.(Lenfestey, Smith et al. 2007) There was no significant difference in baseline WBC between the groups. Neonates with a ventricular catheter and infection had a mean WBC count of 150 cells/mm$^3$.

3. Intraventricular hemorrhage of prematurity

Premature, low-birth weight neonates have a risk of intraventricular hemorrhage. Approximately 57-85% of patients with hemorrhage will develop post-hemorrhagic hydrocephalus (PHH). The complication rate for shunts in these children is high due to an immature immune system, medical co-morbidities, and often thin, tenuous skin.

Many premature children will undergo temporizing procedures prior to placement of a definitive shunt. Temporizing procedures include serial lumbar or ventricular punctures, placement of a ventricular-subgaleal shunt, or placement of a ventricular access device (VAD). These measures allow removal of CSF while the child grows.

The clinician is often faced with a decision of how to interpret data from sample of CSF prior to placing the shunt. Given the prior intraventricular hemorrhage, the CSF may contain elevated levels of red blood cells (RBC), white blood cells (WBC), and protein levels. There is a persistent concern that elevation of cell or protein levels may affect the survivability of a shunt.

There are few laboratory studies evaluating the physical properties of CSF in relation to its cell and protein content. CSF normally has a similar viscosity to water, however its physical properties may be altered by high levels of cells or protein.(Brydon, Hayward et al. 1995) Brydon et al. studied the properties of 126 CSF samples from patients with hydrocephalus of various etiologies. They found that the viscosity of CSF differed from water by 1.4%. At supraphysiologic protein contents, the difference in viscosity was only approximately 6%. (Brydon, Hayward et al. 1995; Brydon, Hayward et al. 1995) In a separate publication, they also demonstrated that CSF protein levels did not impair shunt function, although an elevated RBC count did. An acceptable level of RBCs for safe shunt function was not defined.(Brydon, Bayston et al. 1996) Bloomfield et al. examined the physical properties of CSF by sampling 23 patients undergoing cranial surgery.(Bloomfield, Johnston et al. 1998) In their model, CSF viscosity also did not differ significantly from water over a range of protein contents. Baird et al. studied the effects of fluid with varying concentrations of protein or RBC in the function of a PS Medical (Medtronic, Inc.) valve. They found that protein did not affect valve function but that large numbers of RBCs led to valve failure.(Baird, Farner et al. 2002) Sainte-Rose et al. found no effect on Orbis Sigma valves with solutions containing up to 25 g of protein/liter.(Sainte-Rose, Hooven et al. 1987)

Brydon et al. performed clinical studies after the aforementioned laboratory work. They concluded that an elevated CSF protein count did not statistically increase the risk of shunt complications.(Brydon, Hayward et al. 1996) There are studies evaluating shunting after
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Aneurysmal subarachnoid hemorrhage in adults. Both Rammos et al. and Kang et al. found that shunt malfunction was not statistically related to CSF protein or RBC counts. (Kang, Park et al.; Rammos, Klopfenstein et al. 2008)

It is important to note that results found in adults do not necessarily translate to the preterm child. The brain of a preterm infant significantly differs from that of an adult in the degree of myelination and thus brain compliance. The overall risk of shunt failure in an adult is generally low, however the risk in a preterm infant is high.

We studied 58 low birth-weight, premature infants who developed PHH. (Fulkerson, Vachhrajani et al.) The CSF samples taken within 2 weeks prior to shunt insertion are shown in Table 2. Note that all these children had high numbers of RBCs and WBCs.

Of these 58 patients, ten (17.2%) had shunt failure within 3 months of insertion and nine (15.5%) suffered shunt infection. Both the failure and infection rate were higher for children with PHH compared to our overall rates for all children over the study period. A statistical analysis was performed to see if the shunt failure or infection rate was related to cell count or protein level prior to shunt insertion. Previous case reports have attributed shunt failure to high cell or protein levels. (Foltz and Shurtleff 1963; Lorber and Bhat 1974; Wise and Ballard 1976; Taylor and Peter 2001) Some authors recommend delaying shunt insertion until arbitrary CSF levels are reached. However, we found no statistical relationship of shunt infection or shunt failure with levels of CSF RBCs, WBCs, or protein levels at the time of shunt insertion. (Fulkerson, Vachhrajani et al.) Therefore, the timing of shunt placement should be based on the child’s gestational age, weight, and overall clinical condition.

<table>
<thead>
<tr>
<th>CSF Parameter:</th>
<th>Value:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC/mm3</td>
<td>$3103.5 \pm 9102.4$</td>
</tr>
<tr>
<td>WBC/mm3</td>
<td>$168.8 \pm 1163.6$</td>
</tr>
<tr>
<td>Protein (MG/DL)</td>
<td>$211.1 \pm 158.7$</td>
</tr>
<tr>
<td>Glucose (MG/DL)</td>
<td>$26.3 \pm 12.7$</td>
</tr>
</tbody>
</table>

Table 2. Cerebrospinal fluid values (mean ± standard deviation) of 58 low birth weight-premature infants prior to shunt insertion

4. CSF eosinophilia

As stated earlier, small numbers of leukocytes may be found in the CSF in children. The majority of these are lymphocytes or monocytes; eosinophils are normally absent. Eosinophils are granulocytes produced in the bone marrow and normally found in mucosa. They have a myriad of functions associated with hypersensitivity and inflammatory reactions. Bosch and Oehmichen examined 10,000 qualitative CSF cytological preparations and found eosinophilia in less than 1%. Given the overall rarity of eosinophils, the authors concluded that their presence was pathologic. (Bosch and Oehmichen 1978)

The finding of CSF eosinophils has been associated with allergy, intrathecal antibiotic administration, parasitic infestation, neurophilis, and fungal or tuberculosis infection. (Kessler and Cheek 1959; Bosch and Oehmichen 1978; Traynelis, Powell et al. 1988; Snow and Kossovsky 1989; Vinchon, Vallee et al. 1992; Niggemann, Bauer et al. 1997; Lo Re
It has also been found in patients with hypersensitivity reactions to a shunt, predominately in older tubing materials (Traynelis, Powell et al. 1988; Jimenez, Keating et al. 1994).

While eosinophils are normally absent in patients without shunts, their presence is relatively common after shunt placement. We followed CSF samples after initial shunt placement in 300 children (Fulkerson and Boaz 2008). We identified eosinophilia in 93 of the 300 (31%) patients who underwent placement of their initial shunt. Statistical analysis identified that the risk factors for eosinophilia included a history of intraventricular hemorrhage of prematurity, younger age at shunt insertion, CSF leakage, infection, use of intrathecal antibiotics, and blood in the cerebrospinal fluid.

Shunted patients may have eosinophils in the absence of infection. Eosinophilia occurred within one month of shunt insertion in 69.2% (average 14.6 ± 8.7 days) and was transient in 95% of cases. We found two strong correlations with non-infectious eosinophilia: CSF leakage and intraventricular blood.

There was a statistical relationship of eosinophilia with CSF leakage or fluid accumulation under the skin. This was especially true in patients with the largest numbers of eosinophils.

Figure 1 illustrates the clinical course of a 3-month-old male with a shunt infection. The shunt was removed (Day 0) and an external ventricular drain (EVD) was placed. He has a small eosinophilic reaction to the initial infection. He had a leakage of CSF around the drain site (Day 9 – first vertical line). The eosinophil counts rose dramatically after the leak. He suffered a second leak (Day 15 – second vertical line) and again, the eosinophils rise. This suggests that the eosinophilia is more a reaction rather than a cause of malfunction.

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Fig. 1. **Clinical course of 3-month old with shunt infection.** The patient had leakage of CSF on Day 9 and 15. The number and percentage of eosinophils rose after these two events. (Reprinted with permission from *Journal of Neurosurgery:Pediatrics* 1: 288-295, 2008)
The second correlation of CSF eosinophilia is with the presence of intraventricular blood. We found a statistically significant relationship between eosinophilia and a CSF sample with greater than 100 RBC/mm$^3$.

The intraventricular space is relatively protected. Inflammatory cells are normally not present. CSF leakage exposes this immunologically privileged area to a space with inflammatory cells. Hemorrhage may bring these immunogens into the ventricular space. Eosinophils are known to migrate to areas rich in fibroblasts and enhance tissue remodeling through release of numerous cytokines. (Munitz and Levi-Schaffer 2004) Eosinophils interact with endothelial cells and enhance angiogenesis through growth factors. (Rothenberg 1998; Munitz and Levi-Schaffer 2004)

In our series, patients with CSF eosinophilia had a higher incidence of shunt malfunction compared to the general shunted population. This has also been reported by other authors. (Tung, Raffel et al. 1991) In these patients, the valve or catheter may be blocked with inflammatory debris. Eosinophils are known to propagate many inflammatory responses through secretion of chemicals involved in up-regulating adhesion systems and cellular trafficking. (Rothenberg 1998) This likely promotes the attraction and adhesion of cells, contributing to shunt blockage. The need for shunt revision after initial placement was statistically correlated with the total number and percentage of eosinophils in this series.

5. Shunt infection

Approximately 5-8% of newly placed shunts will become infected. (Drake, Kestle et al. 1998) Clinical signs of infection include shunt failure, fever, abdominal pain, and wound dehiscence. Diagnosis of a shunt infection comes from the appropriate clinical scenario with a positive CSF bacterial culture. The treatment of shunt infection generally includes surgical removal of all existing shunt hardware, temporary CSF diversion, and antibiotics. However, the culture results may not be known for a number of days to weeks. The treating physician may need to make clinical decisions based on interpretation of the CSF sample.

The most common bacterial organisms causing shunt infection are coagulase-negative \textit{Staphylococci} and \textit{Staphylococcus aureus}. Other potential pathogens include \textit{Propionibacterium acnes}, Streptococcal species, and gram-negative organism (\textit{E. coli}, \textit{P. aeruginosa}, \textit{Klebsiella} species, and \textit{Enterobacter} species). CSF samples will often show a rise in the WBC count with a predominance of polymorphonuclear leukocytes (PMNs) in patients with infection from these pathogens.

The WBC count that is diagnostic of infection is unknown. (Kestenbaum, Ebberson et al.; Garges, Moody et al. 2006; Lenfestey, Smith et al. 2007) Previous authors have used a level of 100 WBC/mm$^3$ as a level indicative of infection. (Lan, Wong et al. 2003; Lenfestey, Smith et al. 2007) However, the WBC count in shunt infections is variable. Conen et al. examined 78 shunt infections in patients over 12 years old. While 80% of patient had a CSF leukocyte count greater than $5 \times 10^6$ cells/mm$^3$, a “normal” cell count occurred in approximately 20% of infections. (Conen, Walti et al. 2008) Other markers for infection have been studied, including tumor necrosis factor-$\alpha$, various interleukin concentrations, (Asi-Bautista, Heidemann et al. 1997) and polymerase chain reaction for amplification of bacterial DNA.
(Banks, Bharara et al. 2005) While these show promise, there is not yet widespread acceptance.

The levels of CSF WBC and the differential percentage of PMNs, lymphocytes, monocytes and eosinophils vary depending on the infecting organism (Figure 2). A case example is shown in Figure 3. This figure shows the cell count in a child who presented with a shunt infection with \textit{P. acnes}. Note the high eosinophil count shown in Figure 3A. The child became secondarily infected with \textit{N. flavum}, a gram-negative organism. He spiked a very high WBC count which was predominately PMNs (Figure 3B). His infection cleared and a new shunt was placed. Unfortunately, the new shunt also became infected with coagulase-negative staphylococcus. He had a moderate WBC reaction with a higher percentage of PMNs and lymphocytes.

We evaluated 105 patients with shunt infection. The WBC count and differential of these 105 patients is shown in Table 3. Gram-negative organisms cause an extremely high WBC count with a predominance of PMNs. In our analysis, a differential percentage of greater than 62\% PMNs was most suggestive of a gram-negative infection. Therefore, the treating physician may consider choosing an antibiotic regimen that covers gram-negative organisms in a patient with clinical signs of shunt infection and a CSF sample with a high WBC count with > 62\% PMNs.

Fig. 2. \textbf{Average White Blood Cells (WBC) on diagnosis of shunt infection.} The number of leukocytes varies with infecting organism, with higher numbers for gram-negative pathogens, and low levels for \textit{P. acnes}. (Reprinted with permission from \textit{Journal of Neurosurgery: Pediatrics} 1:288-295, 2008)
Fig. 3. CSF reaction in patient with three shunt infections with \textit{P. acnes}, \textit{N. flavum}, and coagulase-negative staphylococcus. (Reprinted with permission from \textit{Journal of Neurosurgery: Pediatrics} 1: 288-295, 2008)
Table 3. Average white blood cell count and differential based on infecting organism

<table>
<thead>
<tr>
<th>Organism:</th>
<th>Initial WBC count (cells/mm³):</th>
<th>PMN (%)</th>
<th>Lymphocyte (%)</th>
<th>Monocyte (%)</th>
<th>Eosinophil (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>387.9 ± 652.8</td>
<td>48.3 ± 31.6</td>
<td>28.7 ± 24.9</td>
<td>19.4 ± 16.1</td>
<td>3.3 ± 4.0</td>
</tr>
<tr>
<td>S. aureus</td>
<td>574.6 ± 1539.0</td>
<td>56.1 ± 26.3</td>
<td>16.6 ± 15.8</td>
<td>22.9 ± 17.3</td>
<td>5.1 ± 6.8</td>
</tr>
<tr>
<td>P. acnes</td>
<td>110.8 ± 163.9</td>
<td>18.0 ± 38.0</td>
<td>37.2 ± 29.0</td>
<td>33.0 ± 32.7</td>
<td>14.4 ± 24.8</td>
</tr>
<tr>
<td>Streptococcal sp.</td>
<td>913.9 ± 1190.9</td>
<td>66.7 ± 41.9</td>
<td>16.7 ± 20.1</td>
<td>16.6 ± 19.6</td>
<td>3.5 ± 4.0</td>
</tr>
<tr>
<td>Gram-negative sp.</td>
<td>1618.0 ± 3165.9</td>
<td>69.3 ± 31.6</td>
<td>11.9 ± 12.0</td>
<td>15.6 ± 23.1</td>
<td>6.9 ± 13.2</td>
</tr>
</tbody>
</table>

Fig. 4. Peak eosinophil differential percentage of the CSF leukocyte count related to the infecting organism in shunt infections. *P. acnes* infections have a significantly higher eosinophil percentage compared to other pathogens. (Reprinted with permission from *Journal of Neurosurgery: Pediatrics* 1: 288-295, 2008)
More indolent organisms cause less of a CSF reaction. *P. acnes* is a gram-positive, anaerobic diphtheroid that is part of the normal skin flora. This organism may cause shunt infection, however the CSF has a significantly lower WBC compared to other organisms. The diagnosis of *P. acnes* infection may be challenging, as culture growth generally requires anaerobic preparation and extended incubation times (up to 2 weeks). (Rekate, Ruch et al. 1980) *P. acnes* infections have a characteristically high percentage of eosinophils (Figure 4).

The clinician should suspect *P. acnes* in the patient with clinical signs of shunt infection, but with a CSF WBC count < 16 with the presence of eosinophils.

The CSF reaction to infection is similar among all organisms. There is an initial predominance of PMNs, although this is lower in *P. acnes*. This is followed by a rise in monocytes and lymphocytes, with possible influx of eosinophils. The total WBC trends towards zero by two weeks with successful treatment of the shunt infection.

6. Conclusions

Interpretation of CSF samples in children with shunts may help guide clinical decision-making.

Children with hydrocephalus resulting from intraventricular hemorrhage of prematurity are at a higher risk of shunt malfunction and infection compared to other shunted patients. They often have elevated levels of protein in their CSF, however, this is not statistically correlated with subsequent shunt malfunction.

CSF eosinophils may be rarely associated with allergic reactions. Eosinophils are found in up to 31% of patients with a newly placed shunt. Children with eosinophils in the CSF have a higher risk of shunt malfunction. Eosinophilia may be caused by exposure of the immunologically privileged intraventricular space with the skin or blood.

Eosinophils are also seen commonly in children with shunt infections. In addition to the presence of eosinophils, examination of the distribution of CSF leukocytes may provide information in evaluating children with shunt infection. Some pathogens, such as gram-negative organisms cause a very high WBC count with a predominance of PMNs. Others, such as *P. acnes*, have a low WBC count but a high percentage of eosinophils. This is clinically relevant because *P. acnes* may require a longer incubation time with anaerobic culture preparation for diagnosis.

7. References


Description of hydrocephalus can be found in ancient medical literature from Egypt as old as 500 AD. Hydrocephalus is characterized by abnormal accumulation of cerebrospinal fluid (CSF) in the ventricles of the brain. This results in the rise of intracranial pressure inside the skull causing progressive increase in the size of the head, seizure, tunneling of vision, and mental disability. The clinical presentation of hydrocephalus varies with age of onset and chronicity of the underlying disease process. Acute dilatation of the ventricular system manifests with features of raised intracranial pressure while chronic dilatation has a more insidious onset presenting as Adams triad. Treatment is generally surgical by creating various types of cerebral shunts. Role of endoscopic has emerged lately in the management of hydrocephalus.

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