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CURRENT METHODS FOR CSF ANALYSIS AND NEW CELL COUNT TECHNOLOGY

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Jaime Noguez, PhD, Cleveland Medical Center, Case Western Reserve University, discusses advancements in CSF testing.

Illustration by Matthew Taraborrelli

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CEREBRAL SPINAL FLUID TESTING

Current methods for CSF analysis and new cell count technology

By Kirsten Malenke

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Cerebrospinal fluid (CSF) analysis is extremely valuable for the diagnosis of a wide variety of infections, diseases and conditions that affect the brain and spinal cord. A number of different tests can be performed for CSF analysis, involving the hematology, chemistry, microbiology and immunology sections of the laboratory. In a recent interview with *ADVANCE*, Jaime Noguez, PhD, assistant director of Clinical Chemistry at University Hospitals Cleveland Medical Center, and assistant professor of Pathology at Case Western Reserve University, discussed the variety of tests that can be performed for CSF analysis, as well as several advancements in CSF testing.

Generally, CSF is collected in three or more tubes and multiple tests can be run on them. Typically, the first tube goes to hematology for the cell count and differentials. The second tube typically is used for chemistry testing, such as determining glucose and total protein. The third tube typically goes to microbiology or immunology for gram stain and bacterial cultures. If possible, a fourth tube of CSF is collected in the case that any additional testing is needed or the cell count needs to be repeated to rule out a traumatic tap. Collection and specimen quality are very important, Noguez stressed, as a bloody tap can interfere with some of the testing methods.

The particular CSF tests that are ordered depend upon the signs and symptoms of the patient and what the physician suspects the patient may have. Physicians may order multiple tests up front, all of which are run simultaneously, or they may order them sequentially depending on the suspected cause of the illness. "They'll typically order a basic set of tests for CSF analysis such as chemistry tests for glucose and total protein, as well as a cell count and differential, then follow up with a wide variety of other tests depending on those initial test results," Noguez said.

During collection, the opening pressure can be measured and other physical characteristics can be assessed such as CSF color, clarity and viscosity. Normally, CSF is clear and colorless, so labs will observe to see whether it's white, tinged, orange or red. They'll also look to see if it's cloudy, contains particulate matter and whether it's viscous or not. "Some conditions will cause CSF to become very thick and move more like syrup down the tube than CSF," Noguez related.

After the sample arrives to the lab, a number of other tests can be performed. Typically, the hematology lab will look for any cells present in the CSF. "Normally, CSF doesn't have any red blood cells and has very few white blood cells," Noguez said, "so we'll look to see if there are any cells present in the sample. If so, we'll count them and try to differentiate the types of white blood cells that are present—because the relative percentages of each type are indicative of different conditions."

CSF analysis is also useful for the diagnosis of infectious diseases. A variety of tests can be used to detect and identify the microorganisms causing the infection. Labs can perform tests to determine which microorganism is causing meningitis or encephalitis, for example. "We can do tests like Gram stains or cultures in order to see the microorganisms under a microscope—we can even do PCR tests to figure out the specific organism that's responsible for the infection," Noguez said. With PCR, labs can detect the bacterial or viral DNA to identify specific microorganisms.

Chemical Tests

CSF can also be analyzed by a wide variety of chemical tests used to detect or measure chemical substances found in the CSF. "We can test for biomarkers of infection, cancer, autoimmune disease and even brain trauma," Noguez shared.

> **Manufacturers are working to provide an alternative system that gives labs the ability to automate cell counting reliably for clear and colorless samples.**

"When testing for cancer, we're looking for tumor markers, like hCG and alpha-fetoprotein," she continued. However, because many of these tests are not yet FDA approved for testing in CSF, most labs don't perform them in-house—they typically send them out to a reference lab. "Any modification to an FDA approved test for serum, even running a non-approved sample type, changes the regulatory classification of the test to a 'Laboratory Developed Test (LDT),' and most labs don't want to take on the extra work needed to meet the regulatory requirements for validation because it can be quite rigorous," Noguez explained.

In the clinical chemistry section, Noguez's lab performs common CSF tests, such as total protein and glucose, which gives physicians an idea of whether or not a patient has an infection. However, when testing for CSF tumor markers, Noguez's lab always sends them out; they aren't run in-house at all. ▸▸

MATTHEW TARABORRELLI

However, Noguez's lab will run certain tests for autoimmune diseases in-house. "We'll look for oligoclonal banding in a patient's serum and CSF," she said. "Or we'll check their immunoglobulin G levels to see if they have multiple sclerosis or another autoimmune disease that's attacking their CNS. There's a wide range of biochemical tests that we can do on CSF."

Advances in CSF Analysis

According to Noguez, although there aren't many new CSF tests on the market, there have been several advances in diagnostic testing for Alzheimer's disease. "Before, physicians would make the diagnosis based primarily on a progressive mental decline observed over time in the patient, but now they've discovered biomarkers that can help them diagnose Alzheimer's before a patient becomes symptomatic," Noguez said.

Specifically, these tests look for two biomarkers called Tau protein and beta-amyloid. Although these tests are not yet FDA approved and are not available in common hospital labs, according to Noguez, there has been much research effort in this area.

Another area that has received much interest lately is traumatic brain injury testing, though many of these tests are also not FDA approved yet. "There are some CSF biomarkers that can detect small amounts of brain damage even though imaging studies may not show any signs of traumatic brain injury," said Noguez. These tests are being developed for patient populations such as athletes, military personnel or first-responders.

Some of these tests are actually common tests currently used in the lab—tests that measure the ratio of albumin in the CSF relative to the serum, for example. However, there are several new biomarkers, such as neuron-specific enolase, or S100 proteins, Noguez said.

Because these tests are new and not yet FDA approved, they are also not commonly used, though some are available at reference labs. "We currently send out all requests for neuron-specific enolase, tau protein and S100 testing to a reference laboratory," Noguez said. "This type of test is not likely to be offered at your standard community hospital due to the low test order volume and strict regulatory requirements for non-FDA approved assays. But we would definitely consider bringing the testing in-house if FDA approval is obtained and our test volumes continue to increase." Though these tests are still quite rare, Noguez sees them becoming more popular as data continues to be gathered to support their clinical validity.

Cell Count Advances

As previously mentioned, the cell count is one of the very first steps taken for CSF analysis, as it gives physicians a direction towards the diagnosis. "It is not a sole diagnostic factor, but it provides a crucial piece of information for physicians to approach the correct diagnostic path," said George Hong, PhD, from Advanced Instruments. For example, "High white cell counts of neutrophils may indicate that the patient has a bacterial infection. And high white cell counts of lymphocytes may indicate that the patient has a viral, tuberculosis or fungal infection or a cancer recurrence in the central nervous system," Hong related.

However, even before the type of white cell is identified, or differentiated, it is important to first obtain the total cell count. "Any specimen that is above the normal range—for example, for adults, above 5 cells per microliter, means there is a pathology in the CSF," Hong said.

Currently, CSF cell counts are usually performed by manual microscopy using a hemocytometer. "This is because users often feel that the manual method is really the only choice out there for their CSF counts—even though it is labor-intensive and the precision is poor," Hong said. "So the labs are always confronted with having the issue of interpersonal and intrapersonal variability."

Performing a manual cell count is often necessary because many automated hematology analyzers are not able to obtain an accurate cell count of clear and colorless samples with clinically relevant low levels of total nucleated cells (TNCs) and red blood cells (RBCs).[1] These analyzers typically utilize flow-cell based technology, coupled with either optical imaging or scatter diagram.

For RBC counts, some analyzers can only round off the counts to zero or thousands of cells per microliter. In other cases, it is necessary to classify the TNCs and RBCs, and this can result in a problem of subjectivity, Hong said. "That becomes an obstacle for some medical technologists or scientists because sometimes they cannot

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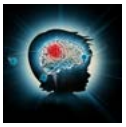

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tell an artifact from an intact cell," he added. "If they classify cells incorrectly, then that means they may report an incorrect count at the low range of cells."

According to Hong, most current hematology analyzers are heavily used for complete blood cell counts (CBC) or urine analysis. When a CSF sample needs to be tested, the users must stop the workflow by changing the mode of analysis by first performing a background check before being able to continue with the analysis. This process takes up unplanned time. "Then it becomes a judgment call for the users to say, 'do I stop it or not stop it, even though I know that the CSF count is an urgent STAT test?'" Hong shared.

"You can see that counting a CSF sample may be a problematic bottleneck for labs," he continued. "Medical technologists know that, when a CSF sample comes in the lab, they should drop what they are doing to perform the count because patients may suffer with the wrong empirical treatment if the correct initial count is not provided in time."

Manufacturers are working to provide an alternative system that gives labs the ability to automate cell counting reliably for clear and colorless samples.[1] Rather than utilizing flow cytometry based technology, the GloCyte Automated Cell Counter System combines fluorescence and microscopy with digital image analysis principles, highly specific reagents and a counting algorithm to deliver accurate RBC and TNC counts with linearity down to 0 cells/µL.[2]

This system only requires a small 30 microliters of sample per test and uses disposable cartridges, minimizing the risk of contamination and effectively reducing the time spent counting difficult CSF samples that could take an hour or more to perform manually. ■

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