State of the art

The Role of Lumbar Puncture as a Diagnostic Tool in 2005

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ABSTRACT

Analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) is fundamental to the management of inflammatory disease of the central nervous system (CNS), particularly that due to infection. This review summarises the role of lumbar puncture, anatomy and pathophysiology of CSF, techniques of obtaining CSF, indications, contraindications and complications of LP, methods of analysis and some of the implications of specific changes in CSF. The CNS is protected by unique immunological barriers, and has some unique responses to processes that breach these barriers. While clues in the epidemiology, history and clinical features of potential CNS inflammatory disease may be important in guiding early empirical treatment which may obviate adverse outcomes, many pathological processes cannot be distinguished or appropriately treated without analysis of CSF.

When appropriate assessments are made of the indications, risks and potential to alter management, LP is a relatively safe procedure with a high diagnostic yield. Optimal performance and use of LP requires individual skill and judgment, and often benefits from close liaison with several disciplines, including emergency, intensive care, diagnostic laboratory, clinical imaging, neurology and infectious/ communicable diseases specialists. Understanding of the sensitivity, specificity and variation of CSF testing is critical to its effective use. Some CSF testing is sensitive, specific and timely, but other CNS disease processes will generate obscure and ambiguous results, and interpretation may benefit from liaison with experienced specialists in several fields. Polymerase chain reaction (PCR) testing has changed the practice of LP and is likely to generate further evolution. Some findings on CSF analysis may have implications beyond the individual patient – the consequences of the diagnosis of meningococcal meningitis, emerging pathogens such as West Nile virus or Nipah virus, and the identification of anthrax meningitis in the USA may be quite profound on both a local and global scale. (**Critical Care and Resuscitation 2005; 7: 213-220**)

Key words: Diagnostic lumbar puncture, procedure, cerebrospinal fluid, review

The procedure of lumbar puncture (LP) to obtain cerebrospinal fluid (CSF) by was pioneered by Quinke in the late 19th century, initially as a therapeutic manoeuvre to treat hydrocephalus.[1] It is now a clinical skill fundamental to the management of infection, inflammation and other pathological processes affecting the central nervous system (CNS). Lumbar puncture is critical for the diagnosis of bacterial, viral or fungal meningitis, and may provide clinically valuable information in encephalitis, myelitis, other inflammatory CNS disease, CNS malignancy and some cases of intracerebral bleeding.[2]

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Delay in initiating appropriate treatment for bacterial meningitis and herpes virus encephalomyelitis is associated with adverse clinical outcome.[3-5] While there are few absolute contraindications to lumbar puncture, the procedure can cause death or serious neurologic injury, and the decision to perform LP should never be undertaken casually or by inexperienced operators.[2]

The CNS is protected by a unique arrangement of anatomical and immunological barriers. As a consequence serious inflammatory disease of the CNS is relatively rare, but may be devastating, both for the individual and the community. Pathologic processes in the CNS have limited pathogenic and clinical expression: different pathogenic processes may cause indistinguishable disease, requiring significantly different therapeutic approaches.[4,5] Analysis of CSF obtained by LP usually provides the most effective means of diagnosis and of determining potential treatment, prognosis and resource allocation in patients with CNS disease. While the history, epidemiology and clinical features may suggest a particular cause of CNS disease, it is rarely possible to exclude other diagnoses, or treat empirically, without both adequate imaging of the brain and analysis of CSF.

The feasibility, safety and usefulness of LP vary with the clinical situation and over time. The emergence of new pathogens (e.g. Nipah virus, variant Creutzfeldt-Jacob disease, etc.), changes in epidemiology of existing pathogens (e.g. West Nile Virus, *Haemophilus influenzae*, bioterrorist anthrax, etc.), the emergence of new diagnostic techniques (e.g. nucleic acid detection and quantification) and new treatments (e.g. acyclovir, gancyclovir, CNS penetrating HIV treatment, etc.) have changed the role of LP and therapeutic responses to abnormalities in CSF.

Anatomy, physiology and pathophysiology of cerebrospinal fluid

The CNS is physically and immunologically isolated within functional barrier systems, the blood brain barrier and blood CSF barrier (BCSFB), a consequence of the anatomy and cellular function of the meninges and arrangements of tight and gap junctions of specialised meningeal epithelial and vascular endothelial structures.[2,6]

CSF is contained in two connected compartments: the cerebral ventricles (lateral, third and forth) communicating with the subarachnoid space through a sequence of narrow foramina (Monro, Sylvius, Luschka and Magendie). CSF is produced by both filtration and active transport (pinocytosis) of components of capillary blood at choroid plexuses in the cerebral ventricles at a maximum rate of approximately 20 mL/hour.[2,6] Total CSF volume in adults is 120 - 150 mL, with approximately 30 mL in the spinal subarachnoid space.[2,6] Diuretics and carbonic anhydrase inhibitors may reduce CSF production. Normal CSF pressure is 50 - 195 mm CSF (3.8 - 15.0 mmHg), though it may be considerably higher in disease.[2]

Flow of CSF is from the choroid plexuses in the ventricles, through the foramina to the subarachnoid space, thence rostrally to the arachnoid villi in the venous sinuses, particularly the superior sagittal sinus, where it is reabsorbed by a combination of active and passive transfer. Both production and reabsorption of CSF are specialised processes that may be affected by both physical obstruction (particularly in the foramina), and pathophysiological processes, such as those occurring in meningeal inflammation due to infection. The opening pressure for the arachnoid villi, projecting through the dura into the venous sinuses, is 20 – 50 mm CSF, but active transport of both fluid and particles larger than erythrocytes (~ 7 μm) through the villous epithelium in giant vesicles provides additional CSF reabsorptive capacity – albeit one subject to limitation in active inflammation.[2] Periventricular swelling, basal meningitis and sagittal sinus venous thrombosis have potent local effects on CSF production, flow and reabsorption, and should be assessed with optimal available imaging techniques (CT, MRI, SPECT or PET scanning) whenever there is consideration of performing LP to obtain CSF in clinical situations where changes in CSF physiology may be occurring.

Techniques of lumbar puncture

LP is usually performed by inserting a bevelled, stylet-occluded, hollow-core (Quinke) needle into the lumbar cistern in the midline, below (or occasionally at) the L3 - L4 interspace, using sterile technique and appropriate skin decontamination and drying time (> 30 seconds). The needle must traverse skin, subcutaneous tissue, supraspinous ligament, interspinous ligament, the ligamentum flavum, the epidural space (containing the internal vertebral venous plexus), the dura and arachnoid to enter the subarachnoid space, a distance of 4 - 8 cm in non-obese adults.[6] The spinal cord ends lower than the L2 - L3 disc in < 1% of adults and slightly lower (L3) in infants.[6] Tuffier's line joins the most superior part of both iliac crests, and usually intersects the midline at the L4 spinous process or L4 - L5 interspace.[6]

By inserting the LP needle over the L5 spinous process in the midline, and aiming for the umbilicus (15° cephalad) with the patient in the lateral recumbent position, the coronal plane of the trunk perpendicular to the floor and the lumbar spine flexed to maximise the interspinous space, it is usually possible to safely pass the needle through the supraspinous and interspinous

ligaments until the resistance of the ligamentum flavum is encountered. The needle should then be advanced in small (~ 2 mm) increments until CSF appears at the hub of the needle on removing the stylet. Reaching the resistance of the vertebral body or causing referred pain in the legs from contact with the cauda equina without seeing CSF indicates failure – a "dry tap". Advancement without an occluding stylet or active aspiration during insertion is associated with increased likelihood of complications, such as trauma to the cauda equina.[6] Use of an atraumatic (Sprotte or Whitacre) or very small bore (< 22 gauge) needle may decrease the rate of complications, but make it difficult to obtain diagnostically useful amounts of CSF, and is not generally recommended.[7] It may be easier to detect entry into the subarachnoid space if the procedure is performed with the patient sitting upright and maximally flexed, but the patient must then be rotated to the lateral recumbent position to measure CSF opening pressure.[6] LP by an experienced radiologist under fluoroscopic or CT guidance is preferable to multiple failed attempts to obtain CSF with conventional technique. Alternative methods for obtaining CSF include cisternal, high cervical (C2) and ventricular approaches, particularly if large volumes of CSF are required, but all require specialised equipment and considerable experience to be performed safely.

Indications for lumbar puncture

LP is essential for the diagnosis of meningitis, and may provide valuable information in encephalitis, myelitis, demyelinating conditions of the CNS (including multiple sclerosis and Guillain-Barre syndrome) and CNS malignancy. The role of LP in the diagnosis of intracerebral haemorrhage and intracranial abscess has been largely superseded by CT and MRI scanning, but the demonstration of a normal (or minimally abnormal) CSF may be of clinical significance in extra-meningeal disease, such as parameningeal abscess or endocarditis.

Since the clinical features of CNS disease (headache, changed mental state, focal neurological signs, fever and /or vomiting) may be subtle, protean and non-specific,[2,5,7-9] CSF analysis is usually essential for diagnosis, and has a high likelihood of providing information which may affect the management and outcome of CNS inflammation, particularly that due to infection. In a recent series of 108 adults presenting to one Australian institution with headache and fever, 25% had abnormal CSF.[10] An older US series found that 14% of LPs for suspected meningitis were abnormal.[11]

Enteroviral meningitis, which has a benign prognosis, is now the most common diagnosis identified by LP in patients presenting with symptoms consistent with CNS infection in most developed countries, but exclusion of serious (and treatable) CNS infections due to HSV, varicella, and the encapsulated bacteria (*Neisseria meningitides, Streptococcus pneumoniae*, *Listeria monocytogenes*, and (increasingly rarely) *Haemophilus influenzae*) usually requires CSF analysis, and can rarely be made on clinical grounds alone.[5,10,12-16] Epidemiologic peculiarities, such as travel and/or arthropod exposure (malaria, Japanese Encephalitis, Murray Valley Encephalitis, West Nile virus, Hantavirus etc.), animal exposure (Hendra, Nipah, rabies, Australian bat lyssavirus etc.) or exposure to a known human contact (HIV, epidemic meningococcus, enterovirus 71, tuberculosis, etc.) may suggest an exotic cause, and should be investigated with LP.

Immunodeficiency states, such as HIV infection, transplantation, neutropenia, hypogammaglobulinaemia, lymphoma and immunosuppressive treatment change the frequency, spectrum and clinical expression of CNS infections, and CSF analysis is usually required for appropriate diagnosis and treatment of possible CNS inflammation.[12,13] Meningitis following trauma or surgery is more frequently associated with microbial pathogens other than the encapsulated bacteria, such as staphylococci (including MRSA and coagulase-negative staphylococci), Gram negative bacteria, fungi or *Nocardia*, and CSF analysis is essential to guide appropriate treatment.[2,12]

Generally speaking, it is reasonable to invoke the maxim that lumbar puncture should be performed whenever it is considered potentially useful – provided there is no significant contraindication.

Contraindications to Lumbar Puncture

Death following LP was first described in 1896,[14] and fear of "coning" due to reduction of lumbar CSF pressure after LP has dogged the use of the procedure, even after the widespread availability of CT scanning significantly changed both the indication for LP (obviating its use to diagnose intracranial haemorrhage) and the ability to detect "brain shift" that predisposes to coning after LP.[15] Notwithstanding the prevalent concern about this complication, the incidence of herniation after LP was reported to be < 1%, even in the pre-CT era. Despite this, recent case reports and experience demonstrate that even pre-emptive CT scanning does not always forestall this complication.[15] While it has been said that there are no absolute contraindications for lumbar puncture,[2] evidence of brain shift raises the possibility of brain herniation and death after LP, whether or not CSF pressure is raised or papilloedema is present.[15]

The term brain shift is preferred to that of raised intracranial (or CSF) pressure, since CSF pressure may

be raised without incurring the risk of herniation on LP.[15] The significance of brain shift depends on where and when it occurs: slowly developing, diffuse swelling is less likely to cause significant direct pressure effect on brainstem structures and cerebral blood flow than that which develops over hours or days in central or lateral parts of the brain.[15] Recent onset of symptoms (particularly headache, vomiting and changes in level of consciousness) and focal cerebral or brainstem signs (including bradycardia or apnoea) are clinical features that should prompt evaluation of possible brain shift by CT (or MRI) before LP. CT features that may indicate brain shift include obliteration of the lateral, third and or fourth ventricles (though the lateral ventricles may be normal or dilated in obstructive hydrocephalus), effacement of sulci and of cisterns, and lateral shift of midline structures or herniation from one intracranial compartment into another, particularly uncal or tentorial herniation.[7,15]

Other relative contraindications to LP include local infection at the site of LP, and significant coagulopathy or thrombocytopenia.[7]

Complications of lumbar puncture

Apart from cerebral herniation and death, major complications of LP include post-lumbar puncture headache (PLPH), local trauma, spinal haematoma and subarachnoid space infection.[2,7] Less common complications include intervertebral disc herniation and discitis, extra-spinal haematoma, cervical spinal cord infarction, cortical blindness, and intraspinal epidermoid tumor due to inoculation of epidermal cells if a non-occluded needle is used.[2] All except PLPH are rare.

PLPH occurs in 20-40% of patients who have LP and is thought to be due to low CSF pressure consequent on leakage from the dura.[2,7] The headache is characteristically postural (relieved by lying flat), usually occurs within 48 hours of LP (though up to 24% begin > 72 hours), and rarely last more than a week.[2,7] Bed rest has not demonstrated any clear prophylactic benefit.[2] The incidence of PLPH decreases with the use of smaller gauge (< 22 gauge) or atraumatic LP needles, but the diagnostic yield of LP diminishes with these measures.[2] Persistent PHLP associated with continued CSF leak may benefit from treatment with an autologous epidural blood patch.[2,7]

Assessing CSF

Measurement of LP "opening" pressure and the gross appearance of CSF should always be recorded if CSF is obtained. Normal lumbar CSF pressure in healthy adults in lateral decubitus position is < 150 mm CSF. LP opening pressures of > 200 mm CSF indicate pathology, though pressures may be transiently increased by the Valsalva maneuver or decreased by hyperventilation during the procedure.[2] Normal CSF is clear and colourless. CSF can be made turbid by as few as 200 leukocytes (WBC)/mL or 400 erythrocytes (RBC)/mL, but requires > 6000 RBC/mL to appear grossly bloody. Bacteria, fungi and epidural fat may occasionally cause a turbid CSF in the absence of cells.[2] Xanthochromia is usually due to lysis of RBC, and begins to appear within 2 - 4 hours of RBC entering the subarachnoid space. CSF protein > 150 mg/dL and hyperbilirubinaemia may also cause xanthochromia.[2,7] Increased CSF viscosity may be seen in severe cryptococcal infection, but is more commonly associated with adenocarcinoma.

Given the difficulties and potential complications of LP it is important to use the CSF obtained appropriately. Decisions regarding what tests should be done on which samples of CSF, with what priority, by which laboratory and with what special handling, transport and notification must all be made before the LP is attempted. This will depend not only on the clinical situation, but also on local conditions and time of day and week. Discussion with Pathologist and/or Infectious Disease specialists is usually appropriate before doing the LP.

Total CSF protein concentration in lumbar CSF of a healthy adult is < 45 mg/dL, with a CSF/serum ratio of albumin of 1:200.[2] Protein is largely excluded from the CSF by the BCSFB, and normally only reaches CSF by pinocytotic transport across choroidal epithelium in the choroid plexus. In CNS inflammation, protein is elevated by a combination of leak into the CSF through disruption of the venular endothelial tight junctions and impaired active clearance through the arachnoid villi. Immunoglobulins are normally excluded from the CSF, with a CSF/serum ratio of >1:500, and is essentially all IgG, actively transported across the BCSFB by a process which requiring 3 - 6 days to reach equilibrium in normal adults [2]. Oligoclonal IgG bands present in CSF, but not in serum, suggest immune response within the CNS, and may be seen in a variety of acute and chronic CNS infections and in other conditions, including multiple sclerosis.[2] Increased CSF protein is the most common and least specific of CSF alterations in disease, and is seen in CNS infections, haemorrhage, Guillain-Barré syndrome, and occasionally in myxoedema and diabetic neuropathy. CSF protein levels of > 200 mg/dL suggest bacterial infections,[17] and levels of > 500 mg/dL have been described in tuberculous meningitis, arachnoiditis and spinal block.[2,7] In subarachnoid haemorrhage or traumatic tap, red blood cells may raise CSF protein by roughly 1 mg/dL per 1,000 RBC.

Table 1. Minimal volumes of CSF required for common diagnostic tests.

Test	*Volume required*	*Comments*
Cell count & differential	0.5 - 1 mL	
Glucose & protein	0.5 mL	+ simultaneous serum sample
Gram stain & bacterial culture	2 - 5 mL	larger volumes → ↑ yield
Viral PCR ± culture	1 - 2 mL	
Cytospin or flow cytometry	2 - 5 mL	
Mycobacterial &/or fungal cultures	~ 20 mL	low yield for smaller volumes
PCR for mycobacteria	1 - 2 mL	
Cryptococcal antigen	0.5 mL	+ simultaneous serum sample
VDRL or Wasserman	0.5 mL	+ simultaneous serum sample
Oligoclonal bands &/or serology	> 2 mL	+ simultaneous serum sample

CSF glucose is normally approximately 65% of serum glucose. CSF glucose is depressed in approximately 50% of patients with acute bacterial meningitis, most patients with tuberculous and fungal meningitis, and ~25% of patients with mumps and herpetic meningitis. It may also be depressed in systemic lupus erythematosus, rheumatoid meningitis, sarcoidosis and CNS malignancies.[2,7]

CSF cell count must be performed manually by an experienced operator using a Neubauer chamber within 30 minutes of sampling, since cell counts diminish after this time due to settling, binding to tube surfaces and cell lysis.[2,7] Normally, CSF contains fewer than 5 WBC/mL, most of which are small lymphocytes. In adults, the presence of any neutrophils should be regarded with concern, though one or two may be found in otherwise normal CSF, and small numbers (< 10/mL) may occur in non-infective conditions, such as infarction, trauma or post-myelography.[2,7] Normal neonates may have up to 10 WBC/mL, up to 60% of which may be neutrophils.[2] It is usually possible to distinguish polymorphonuclear (PMN) leukocytes (neutrophils and eosinophils) from RBCs and monocytic cells by phase contrast microscopy during cell counting, however only specific differential staining (e.g. Wright stain) will allow distinction of eosinophils from neutrophils and of lymphocytes from monocytes or some fungi. In the event of a traumatic tap, a correction of 1 WBC per 700 RBC /mL allows some estimation of CSF pleocytosis, but cannot be relied on in the presence of anaemia or leukocytosis.[7]

Differential cell counting is usually performed on CSF concentrated by filtration or centrifugation. Normal adult CSF may contain up to 15% neutrophils on differential staining of concentrated samples, but small lymphocytes predominate, with occasional large lymphocytes and other monocytes in concentrated specimens. Plasma cells and eosinophils should not be present in normal CSF.[2,7]

While a neutrophilic CSF pleocytosis is the most common abnormality seen with bacterial meningitis, and a predominantly monocytic or lymphocytic pleocytosis is more characteristic of viral infection, neither is diagnostic: neutrophil predominance may occur early in viral ("aseptic") meningitis, and monocytes may come to dominate late bacterial infection, particularly in more indolent processes such as *Listeria monocytogenes* meningitis or *Nocardia* cerebritis. Tuberculosis and fungal infections classically show a predominance of lymphocytes. CSF eosinophilia is rare, and should raise the possibility of parasitic meningitis (*Taenia, Angiostrongylus, Gnathostoma, Trichinella, Ascaris, Toxoplasma, Toxocara*), CNS lymphoma or rare manifestations of CNS tuberculosis, syphilis, *Mycoplasma,* fungal infection, rickettsiosis, lymphocytic choriomeningitis virus infection, subacute sclerosing panencephalitis (measles virus), reaction to intrathecal material (e.g. shunts, antibiotics or chemotherapy) or idiopathic eosinophilic meningitis.[2,7]

Gram stain of CSF may provide crucial information for managing bacterial meningitis, but is dependent on the skill of the diagnostic laboratory, the number and type of the organisms present in CSF and when the sample is taken with respect to antimicrobial administration. In general, a careful examination of a correctly prepared Gram stain of a concentrated specimen of CSF is positive in 60 - 80% of untreated patients with bacterial meningitis but half that proportion in previously treated patients.[2,7] The sensitivity of the Gram stain varies, to some extent, with the infecting organism. Organisms may be detected in up to 90% of cases of pneumococcal or staphylococcal meningitis, 80% of *Haemophilus influenzae*, 75% of *Neisseria meningitidis* and fewer than 50% of cases of bacterial meningitis due to other Gram negative organisms, anaerobes, or *Listeria monocytogenes*.[2]

The sensitivity of **acid-fast staining** depends on the skill and persistence of the examiner and on the amount of CSF concentrated. Acid-fast bacilli (AFB) have been detected in up to 87% of cases when large volumes (20

mL) of CSF from 4 different LPs, but fewer than 3% of cases of single, small volume (1 - 2 mL) are examined.[2] Mycobacterial culture and nucleic acid amplification are more sensitive, but may require up to 6 weeks to return a positive result. India ink preparations may detect cryptococcal capsules in up to 75% of patients with HIV-associated cryptococcal meningitis, but only about 50% of HIV negative patients. Cryptococcal antigen detection is more sensitive, but requires laboratory expertise to interpret accurately.[2,7] Phase contrast examination of wet mount preparations may identify motile trophozoites in patients with amoebic meningitis.[2]

CSF culture remains the cornerstone for establishing bacterial and fungal diagnosis, and for determining antimicrobial sensitivity and resistance. A minimum of 2 mL of CSF should be inoculated into enrichment broth and plated onto a variety of media as soon as possible in order to avoid loss of fastidious organisms, such as *N. meningitidis*, *H. influenzae* or anaerobes. Mycobacterial and fungal cultures require 20 - 40 mL of CSF to provide reasonable sensitivity, which usually requires several LPs. Mycobacterial culture may take 6 weeks or longer to become positive, and yields are between 50 and 80%.[2] *Cryptococcus neoformans* and *Candida* species are more easily cultured from moderate volumes of CSF (10 - 20 mL) than other pathogenic fungi.[2] While tissue culture has been the traditional means of diagnosing viral CNS infections, this technique is often slow, resource intensive and expensive, and recovery rates may be poor, particularly in encephalitis.[2] Nucleic acid testing, usually using polymerase chain reaction (PCR), has now replaced tissue culture for most viral CNS disease.

PCR testing requires a specialised and experienced molecular laboratory, and most results are reported as experimental, since the techniques and primers used are usually developed "in house", however the speed (hours to days) and sensitivity has lead to its widespread use, particularly in suspected enterovirus or herpesvirus infection. PCR methods are widely available for enteroviruses, herpes simplex (HSV) 1 & 2, varicella zoster (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), JC virus (JCV), and the arboviruses, such as Japanese encephalitis (JE), Murray Valley encephalitis (MVE) and West Nile Virus (WNV).[2,5,16] Experimental PCR detection techniques have been developed for emerging CNS viruses, such as Nipah, Hendra, and Australian Bat lyssavirus. Quantitative human immunodeficiency virus (HIV) PCR of CSF has been used to estimate the CNS viral "load" in patients with primary HIV infection, and in suspected HIV-associated dementia.[17] In addition to diagnosing JCV, which causes the rare condition of progressive multifocal leukoencephalopathy (PML), PCR may be of use in determining the presence of two other "slow" CNS viral infections: subacute sclerosing panencephalitis (SSPE) caused by measles virus, and tropical spastic paraparesis (TSP) caused by human T lymphotropic virus type 1 (HTLV-1).[2]

PCR methods have also been used for diagnosis of CNS infection with *N. meningitidis*, *S. pneumoniae*, *H. influenzae, Mycobacterium tuberculosis* (MTb), *M. avium* complex (MAC), *Toxoplasma gondii*, *Tropheryma whippelii* (Whipple's disease), *Borrelia burgdorferi* (Lyme disease), *Bartonella henselae* (Cat Scratch disease) and some rickettsial spotted fever infections.[2,16] The sensitivities of these tests may be quite high (> 90% for the bacteria, 60 - 87% for the mycobacteria), but the usual caveats regarding the lack of standardisation, expense, and requirement for specialised laboratory expertise apply. At present PCR techniques have been less useful in the diagnosis of fungal CNS infection, mainly due to the ubiquity of fungi in the environment and consequent high false positive rates.[2]

CSF antigen testing is mainly of use in cryptococcal CNS infection, with a sensitivity of 80 - 95% and good specificity, particularly if pronase is used to digest rheumatoid-like factors that may be present in CSF.[2] Bacterial antigen testing has been developed for *H. influenzae* type b, *N. meningitidis*, *S. pneumoniae*, *E.coli* K1, and group B *Streptococcus*, however these tests are generally less sensitive and more unreliable than Gram stain and culture, and are now rarely used.[2,7] Specific bacterial antigen testing may be of use in partially treated meningitis in which the initial Gram stain and culture are negative.

Measuring **specific antibody levels in CSF** may be of use in arbovirus infections (e.g. IgM to West Nile virus), HIV and other viruses, *Toxoplasma gondii*, neurosyphilis, and occasionally in MTb in high - prevalence populations and to diagnose CNS histoplasmosis or coccidioidomycosis, but are not first line diagnostic methods.[2] CSF antibodies to measles and HTLV-1 may be useful in cases of possible SSPE or TSE.

Other specific testing methods that have been used on CSF include quantification of **lactic acid, C-reactive protein (CRP), adenosine deaminase, TNF-α, IL-1β** and the specialised analytic techniques of **gas-liquid chromatography** and **magnetic resonance spectroscopy** (*in vitro* and *in vivo*). With the possible exception of cytokine measurements, these tests have not yet established a place in routine clinical use.[2]

Detection of **14-3-3 protein** in CSF may be a marker for Creutzfeldt-Jacob disease (CJD) in an appropriate clinical setting, but may also be present in other neurological conditions.[2]

CSF is rarely assessed in isolation. Cultures of blood, urine, sputum and other sites, biochemistry, blood count and film, inflammatory markers (ESR, CRP), immunological testing for autoantibodies and (particularly) imaging techniques such as CT and MRI may be as vital as CSF examination for the diagnosis of a patient presenting with symptoms consistent with CNS disease. Encephalopathy due to systemic infection is more common than primary CNS infection, and LP is seldom the optimal means of diagnosing infective endocarditis, malaria, typhoid, rickettsial disease, urosepsis, gastrointestinal or hepatic abscess. On the other hand, LP may provide important diagnostic clues in some systemic processes, such as vasculitis, SLE, sarcoidosis, Behçet's syndrome, Whipple's disease, drug-induced hypersensitivity syndromes (e.g. non-steroidal anti-inflammatory agents), toxin-mediated syndromes (e.g. tetanus or botulism), or malignancy.

Measuring specific IgM or IgG responses in serum may be very useful in determining the cause of CNS infection, but usually only retrospectively. Serum for antibodies to *Mycoplasma, Chlamydia, Legionella*, enterovirus, adenovirus, influenza, pertussis, HIV, syphilis, HSV, VZV, EBV, CMV and toxoplasma should be tested in patients presenting with meningitis, encephalitis or myelitis without an overt aetiology, since a single high IgM titre may suggest a cause and affect treatment. Other serology which may be indicated if the clinical and epidemiological circumstances warrant include that for arbovirus, *Rickettsiae*, *Coxiella* (Q fever), *Leptospira*, *Bartonella*, *Borrelia* (Lyme disease), *Erlichia* and some parasites, such as *Taenia* (cysticercosis), *Echinococcus* (hydatid disease), *Strongyloides*, *Angiostrongylis*, and *Toxocara*. Post-infectious syndromes, such as encephalomyelitis or transverse myelitis, may follow clinically trivial infections (or immunisation) for which the only clue may be seroconversion.[12]

Conclusions

Lumbar puncture is a fundamental tool in the management of possible infection and other inflammatory conditions of the CNS. When appropriate assessments are made of the indications, risks and potential to alter management, LP is a relatively safe procedure with a high diagnostic yield. Appropriate assessment includes a thorough history and examination, looking particularly for epidemiologic clues to unusual pathogens (e.g. travel, possible contact with infected humans, animals or insect vectors, or immunodeficiency), symptoms or signs of focal neurological dysfunction, and (usually) imaging of the CNS to exclude brain shift. Optimal performance and use of LP requires individual skill and judgment, and often benefits from close liaison with several disciplines, including Emergency Medicine and Intensive Care specialists, diagnostic laboratories and pathologists, clinical imaging specialists, neurologists and infectious or communicable diseases specialists.

Given the potential for preventing adverse clinical outcomes with early treatment of CNS infection or inflammation, current practice often involves empirical treatment of patients presenting with clinical features of meningitis or encephalitis with combinations of CNS-penetrating antimicrobials (such as ceftriaxone and ampicillin and/or vancomycin) and acyclovir. LP may have a an important role in informing appropriate modifications to empirical treatment, in decisions of whether or not to use adjunctive treatments such as corticosteroids, and in providing prognostic information to the patient, contacts, carers and the community. LP will also have a role in monitoring disease course and therapeutic effects. An understanding of the sensitivity, specificity and variation of CSF testing is critical to its effective use. PCR testing has changed the practice of LP and is likely to generate further evolution.

Finally, it is important to recognise the potential public health implications of some LP findings. The rapid confirmation of meningococcal or *H. influenzae* meningitis may allow both appropriate treatment of the index patient and the prevention of other cases by prophylaxis or immunisation of contacts. The diagnosis of anthrax meningitis in the USA in 2001 has had significant, if indirect, effects of the practice of medicine globally, as the implications of covert release of biological weapons were recognised.[18] A less heralded, but potentially more profound implication can be found in the changing epidemiology of CNS arbovirus infections, such as Japanese encephalitis and Nipah virus in Southeast Asia, and West Nile virus in North America. Lumbar puncture is likely to remain a cornerstone of CNS investigation and a fundamental clinical tool for the foreseeable future.

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