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Cerebrospinal fluid: history, collection techniques, indications, contraindications and complications

Líquido cefalorraquidiano: história, técnicas de coleta, indicações, contraindicações e complicações

João Paulo S. Oliveira; Natalia T. Mendes; Álvaro R. Martins; Wilson Luiz Sanvito

Hospital Santa Casa de São Paulo, São Paulo, São Paulo, Brazil.

ABSTRACT

This article is based on a historical review of the medical literature with the purpose of acknowledging the historical stages and anatomical findings over the years, which led gradually to performance of the first lumbar puncture by Quincke, as well as collection techniques and analyses, allowing it to be an irreplaceable diagnostic tool in daily clinical practice. Cerebrospinal fluid analyses have continued to develop and nowadays play a major role in diagnosing and understanding the physiopathology of a great variety of neurological conditions. Biomarkers and genetic sequencing have recently been the target of multiple studies and are implicated as promising diagnostic tools of a large range of diseases.

Key words: cerebrospinal fluid; history; spinal puncture.

RESUMO

Este artigo se baseia em uma revisão histórica da literatura médica cujo objetivo foi reconhecer as etapas e os achados anatômicos ao longo dos anos do desempenho de Quincke – desde a primeira punção lombar –, bem como as técnicas e as análises de coleta que permitiram que essa punção se tornasse uma ferramenta insubstituível na prática clínica diária. As análises do líquido cefalorraquidiano continuaram se desenvolvendo e hoje desempenham um papel importante no diagnóstico e na compreensão da fisiopatologia de diversas condições neurológicas. Recentemente, biomarcadores e sequenciamento genético foram objeto de vários estudos e são considerados técnicas de diagnóstico promissoras para uma grande variedade de doenças.

Unitermos: *líquido cefalorraquidiano; história; punção espinhal.*

RESUMEN

Este artículo se basa en una revisión histórica de la literatura médica cuyo objetivo fue reconocer las fases y los hallazgos anatómicos a lo largo de los años que condujo gradualmente a la primera punción lumbar por Quincke, así como las técnicas y los análisis de recolección; esa punción se ha convertido en una herramienta insustituible de diagnóstico en la práctica clínica diaria. Los análisis del líquido cefalorraquídeo se desarrollaron y hoy tienen un papel importante en el diagnóstico y en la comprensión de la fisiopatología de varias condiciones neurológicas. Recientemente, los biomarcadores y la secuenciación genética fueron objeto de varios estudios y son considerados técnicas de diagnóstico prometedoras para muchas enfermedades.

Palabras clave: *líquido cefalorraquídeo; historia; punción espinal.*

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INTRODUCTION

The cerebrospinal fluid (CSF) is a dynamic, metabolically active substance that has many important functions. Initial studies about it date from the Hippocratic era, and the first lumbar puncture (LP) was performed in 1891 by Quincke to relieve increased intracranial pressure in children with tuberculous meningitis[1]. Collection techniques and analysis have developed substantially in the past centuries, but LP remains a simple procedure and an important diagnostic aid in the evaluation of a large variety of infectious and noninfectious neurologic conditions.

This article reviews the evolution of the CSF analysis over time, as well as the technique, indications, contraindications, complications of LP and the new findings and perspectives for a near future.

HISTORICAL DEVELOPMENT OF LP WORLDWIDE

The study on the CSF starts with the comprehension of its anatomical boundaries and its role on the right functioning of the brain, medulla and meninges. The earliest descriptive accounts of fluid inside brain cavities are found in Edwin Smith's surgical papyrus, probably written in the 17th century BC[2]. Hippocrates made reference to the *falx cerebri* and carried out the first *post-mortem* ventricle access by needle, between 430 and 350 BC. A description of the meninges and ventricles was written by several physicians of the city of Alexandria in the subsequently centuries, based on brain dissections[3].

In the second century AC, Galen (Claudius Galenus) reports that the ventricles of the brain were filled with a clear fluid – described as a vaporous humor and a vital gaseous spirit – which he surmised provided energy for the whole body. This finding delayed the recognition and the analysis of the CSF at the time, once it was believed to be a life-determinant fluid[4]. A more detailed and accurate anatomical report was not known until 1543, when Andreas Vesalius (1543)[5] described the ventricular system; his work was continued by Giulio Aranzi, who published, in 1587, the existence of the choroid plexus and a passage leading from the third to fourth ventricle[6] – afterwards named aqueduct of Sylvius. In 1764, Domenico Cotugno recognized the continuity between cerebral and spinal fluids, as well as the subarachnoid space, after performing post-mortem studies with puncture and anatomical dissections[3] – this was the beginning of the modern CSF physiology. Sixty years later, François Magendie gave the name of CSF to the liquid found in the ventricles and subarachnoid space[7, 8]. Hubert von Luschka complemented his work describing, in 1854, openings on the fourth ventricle through which CSF flowed into the subarachnoid space[9] (named, later, after him "foramina of Luschka"); he also found evidence that CSF was produced by the choroid plexus. In 1876, an accurate demonstration of CSF formation, flow and absorption was made by Axel Key and Gustav Retzius[10].

Heinrich Quincke performed the first LP in vivo in 1891[1], while he was searching for a safe way to remove excess fluid in children with hydrocephalus. He used a needle and a scalpel, and his studies included the measurement of intracranial pressure, protein and glucose levels, cytological and bacteriological analysis. This was an important milestone in the evolution of the CSF analysis and the procedure began to be used routinely for diagnostic purposes.

Along with Quincke's contribution, the previous progress in the field of microbiology – such as cultivating bacteria, Gram staining method and Ziehl-Neelsen stain for identifying the tuberculosis bacillus – made the diagnosis of meningitis possible and more accurate.

In 1902, Millian and Chiray[11] used the term "xanthochromia" for the first time to describe a yellow pigment observed in the supernatant CSF in cases of subarachnoid hemorrhage. Two years later, Henri Dufour (1904)[12] turned diagnostic cytology of the CSF possible with the development of technology to identify neoplastic cells. In 1906, August von Wasserman and Plaut[13] applied Wasserman's serological test (Wasserman's reaction) to the CSF for the diagnosis of syphilis. In 1912, William Mestrezat[14] made the first detailed description of the chemical composition of CSF.

A great innovation came in 1912, when Karl Friedrich Lange[15] developed the colloidal gold test, a qualitative CSF protein study that was able to identify the CSF gamma globulin levels. Its corresponding curves had a specific shape in neurosyphilis and multiple sclerosis, which was called "dementia paralytica formula".

Thirty years later, Elvin Kabat *et al*. (1948)[16] applied the electrophoretic techniques (developed by Hesselvik in 1939) to the CSF analysis and confirmed the increase in gamma globulin fractions in both neurosyphilis and multiple sclerosis. Moreover, they established reference ranges for these analytes and showed that the changes in CSF levels were independent of those in serum, suggesting that immunoglobulins were produced within the central nervous system (CNS) in such diseases. In the middle

of the 19th century, the development of electrophoresis techniques allowed the recognition of fractions of gamma globulins with different mobility in agar gel that appeared as visible bands, named oligoclonal bands by Christian Laterre[17, 18]. The demonstration of oligoclonal bands by the isoelectric focusing method was first reported in 1970. They were selected as the most reliable marker for multiple sclerosis by Hans Link; it is a finding detectable in more than 95% of patients, even though it can also be found in other diseases.

In Brazil, the CSF studies began at 1897, after Miguel Couto carried out the first LP *in vivo* in the country. In 1928, Cerqueira da Luz and Waldemiro Pires performed more than 5,000 cisternal punctures, contributing worldwide for the inclusion of this approach in daily practice[19]. Ten years later, Oswaldo Lange published the first Brazilian book on the subject: "Cerebrospinal fluid in clinics" and was labeled the greatest specialist in the field in the country. In 1940, he released his work "Cerebrospinal fluid syndrome in encephalomeningeal cysticercosis", with substantial impact all over the world[20].

França Netto continued Lange's works, founded the Center for Neurological Investigations focused on CSF studies and, in 1960, brought to Brazil new technologies, such as the accelerated gravitational sedimentation chamber for cytomorphological examinations and electrophoresis[21]. He was a great researcher in neurocysticercosis and other infections of the CNS. In 1972, Soares founded his own CSF laboratory, which is now one of the largest laboratories in Brazil. Carvalho started his studies in 1988 and is, nowadays, the greatest specialist on neuroschistosomiasis in Brazil[19] (**Figure 1**).

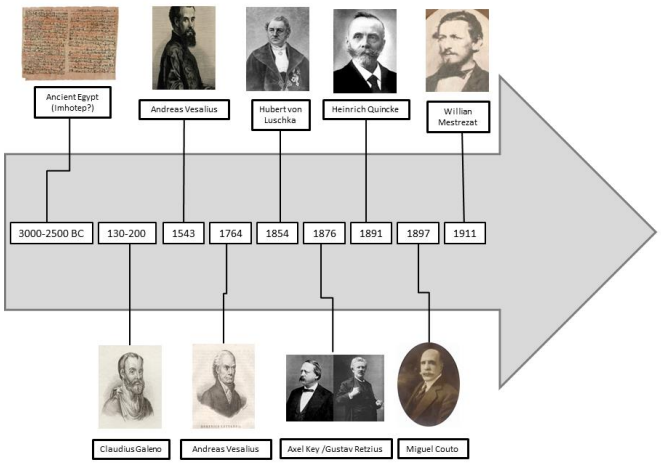

FIGURE 1 – *Authors who contributed to the development of CSF puncture*
CSF: cerebrospinal fluid.

DESCRIPTION OF THE LP TECHNIQUE

An LP can be performed with the patient in the lateral recumbent or prone position, or sitting upright. The lateral recumbent or prone positions are preferred over the upright position because they allow more accurate measurement of the opening pressure.

Description of LP in lateral decubitus:

1. patient in lateral decubitus, knees flexed towards the chest (fetal position);

2. the correct level of entry of the spinal needle is most easily determined with the patient sitting upright or standing. The highest points of the iliac crests should be identified visually and confirmed by palpation; a direct line joining these is a guide to the fourth lumbar vertebral body. However, this line may intersect the spine at points ranging from L1-L2 to L4-L5[22], and tends to point to a higher spinal level in women and in obese patients[23]. The lumbar spinous processes of L3, L4, and L5, and the interspaces between them can usually be directly identified by palpation. The spinal needle can be safely inserted into the subarachnoid space at the L3-4 or L4-5 interspace, since this is well below the termination of the spinal cord;

3. asepsis and antisepsis of the skin are performed with alcoholic solution or chlorhexidine, placement of sterile fenestrated field and shoeing of sterile gloves;

• optional: an anesthetic button can be performed with xylocaine or lidocaine without vasoconstrictor;

4. puncture should be performed with specific needles for LP – the choice of needle type (cutting versus atraumatic) and bore size can influence the risk of a post-LP headache, but also may increase the technical difficulty of the procedure. Make sure that the mandrel completes the needle fully and that it slides correctly into its mandrel;

5. introduction of the 20- or 22-gauge spinal needle midway between the spinal processes of the vertebrae. The needle is oriented rostrally to umbilical scarring with an angulation of approximately 10 to 15 degrees, without lateral deviation;

6. if the needle touches a bone, it should be withdrawn to the subcutaneous tissue and reintroduced with greater or lesser angulation to the initial one;

7. a well-directed needle slides easily through the tissues; a firm resistance is felt in the yellow ligament, followed by a slight resistance when it goes through the dura and arachnoid. The needle should always progress with the mandrel inside, completely inserted;

8. by withdrawing the mandrel, the CSF begins to flow. If this does not occur, being in the subarachnoid space, a root or filament of the dura may be clogging the needle. The needle should be rotated about 90 degrees;

9. fluid is then serially collected in sterile plastic tubes. A total of 8 to 15 ml of CSF is typically removed during routine LP. However, when special studies are required, such as cytology or cultures for organisms that grow less readily, 40 ml of fluid can safely be removed;

10. aspiration of CSF should not be attempted as it may increase the risk of bleeding[24] and lesion of roots. The stylet should be replaced before the spinal needle is removed, as this can reduce the risk of post-lumbar puncture headache;

11. the currently accepted upper limit of normal recumbent CSF opening pressure is 18-20 cm CSF in adults[21, 25]. Studies with volunteers during continuous CSF pressure monitoring and patients during spinal anesthesia report an upper limit of 25 cm CSF[26]; a recent study of adults with peripheral nervous system or psychiatric diseases with normal brain magnetic resonance image (MRI) and magnetic resonance venography found an upper limit of 20 cm CSF[27]. Furthermore, the influence of body mass index (BMI) on CSF opening pressure remains controversial;

• a reference range for CSF opening pressure in children undergoing diagnostic LP has not been established[28]. In a study carried out with 197 children, the threshold for an abnormally elevated opening pressure, determined on the basis of the 90th percentile for all patients in the reference population, was 28 cm of water[29];

12. after collecting the CSF, the needle is withdrawn with or without the introduction of the mandrel;

13. no trials have shown that bed rest following LP significantly decreases the risk of post-LP headache compared with immediate mobilization[30, 31]. It is usually recommended, however, that patients stay at rest for a few hours and drink plenty of fluids. It is worth mentioning that approximately 10%-30% of patients, even with all the necessary precautions, may present headache (**Figure 2**).

INDICATIONS

LP is essential for the diagnosis of bacterial, fungal, mycobacterial, and viral CNS infections and, in certain settings, is also useful for the diagnosis of subarachnoid hemorrhage, malignancies, demyelinating diseases and Guillain-Barré syndrome.

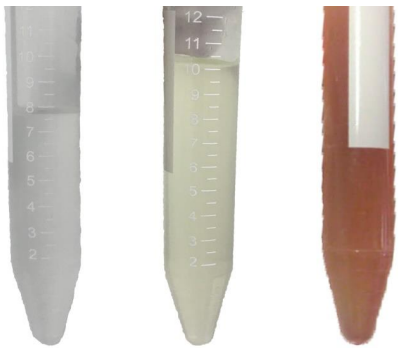

FIGURE 2 – *Visual aspects of CSF: clear, cloudy and hemorrhagic CSF: cerebrospinal fluid.*

The number of definite indications for LP has decreased with the advent of better neuroimaging procedures, including computed tomography (CT) scans and MRI, but urgent LP is still indicated to diagnose two serious conditions: CNS infection (with the exception of brain abscess or a parameningeal process) and suspected subarachnoid hemorrhage (SAH) in a patient with a negative CT scan[32, 33].

A nonurgent LP is indicated as a complementary tool for the diagnosis of the following conditions: idiopathic intracranial hypertension (pseudotumor cerebri), carcinomatous meningitis, tuberculous meningitis, normal pressure hydrocephalus, CNS syphilis and CNS vasculitis. Conditions in which LP is rarely diagnostic but still useful include: multiple sclerosis and paraneoplastic syndromes.

LP is also required as a therapeutic or diagnostic maneuver in the following situations: spinal anesthesia, intrathecal administration of chemotherapy, intrathecal administration of antibiotics, injection of contrast media for myelography or for cisternography[32-34].

CONTRAINDICATIONS

Although there are no absolute contraindications to performing the procedure, caution should be used in patients with: possible raised intracranial pressure[35], suspected spinal epidural abscess[36] and thrombocytopenia or other bleeding diathesis[37].

The British Committee for Standards in Haematology, Blood Transfusion Task Force, produced guidelines suggesting a platelet count of 50,000/µl or more to safely proceed with LP[37]. A low platelet count may be associated with devastating neurological complications due to spinal bleeding. Furthermore, if a traumatic tap occurs, leukaemic cells circulating in the blood may enter into the CSF, thereby possibly worsening the patient's prognosis[38].

Ruell *et al*. (2006)[39] reported 738 LP procedures at Royal Manchester Children's Hospital between March 2001 and June 2005, in 54 pediatric patients. All patients underwent LP and intrathecal chemotherapy under general anaesthetic conditions, and procedures were performed by experienced clinicians (consultants or specialist registrars), according to the national guidelines. No bleeding or neurological complications were observed in any of the patients. Regression curve analysis showed no correlation with platelet count and red cell count in the CSF. This study and existing evidence in the literature would support the safety of performing LPs with platelet counts ≥ 30,000/μl[37-39].

COMPLICATIONS

LP is a relatively safe procedure, but minor and major complications can occur even when standard infection control measures and good techniques are used. The most common complications are backache, headache, radicular pain and paraparesis[40]. We will describe each one of them below.

Post dural puncture headache

The incidence of post dural puncture headache (PDPH) varies widely, depending on patient and procedural risk factors. The incidence of PDPH after spinal anesthesia is generally lower than 3%, but may occur in up to 9% of cases, depending on the type and size of the needle used[41-43]. PDPH after LP occurs in approximately 11% of cases when a standard, traumatic needle is used[44].

The precise etiology of headache after dural puncture is unclear, but three pathophysiologic mechanisms have been proposed: 1. CSF hypotension results in compensatory meningeal venodilation and blood volume expansion, with headache caused by acute venous distention[45,46]; 2. intracranial hypotension related to CSF leak may cause sagging of intracranial structures and stretch of sensory intracranial nerves, causing pain and cranial nerve palsies[47]; 3. altered craniospinal elasticity after LP results in increased caudal compliance relative to intracranial compliance and acute intracranial venodilation in the upright position[48].

Common patient risk factors for PDPH are female sex (two to three times increased risk)[49,50], pregnancy[50-52], a prior history of headache[53,54] and age between 18 and 50 years[55]. Low opening pressure during LP may also predict an increased risk of PDPH[56]. The effect of BMI on the risk of PDPH is controversial in the literature[57-60].

The choice of spinal needle and procedural factors can affect the risk of PDPH. The use of pencil point (atraumatic) spinal needles reduces the risk of PDPH compared with cutting needles of the same size[61,62], and larger conventional needle size is correlated with an increased incidence of PDPH[63].

In addition to procedure modification, a number of strategies have been used to attempt to prevent PDPH after dural puncture. Despite common recommendations for bed rest following dural puncture, this remedy has not been shown to significantly decrease the risk of PDPH[30,64,65].

Small trials have reported that prophylactic administration of epidural morphine, intravenous (IV) cosyntropin, and IV ondansetron may reduce the incidence of PDPH after obstetric anesthesia[66-69]. But ondansetron may trigger migraine headache in susceptible patients[70], and further research is needed to elucidate the role of these drugs in PDPH prevention. In obstetric and general surgical populations, oral caffeine has not been shown to prevent PDPH after dural puncture[71,72].

Epidural blood patch (EBP) is an effective treatment for PDPH, and may also be performed prophylactically, before a headache occurs, after an inadvertent dural puncture. A review of the literature of prophylactic EBP in obstetric patients found that it does not appear to decrease the incidence of PDPH, but may decrease the intensity and/or duration of symptoms[73].

Meningitis

Meningitis is an uncommon complication of LP. The most commonly isolated causative organisms were *Streptococcus salivarius* (30%), *Streptococcus viridans* (29%), alpha-hemolytic streptococcus (11%), *Staphylococcus aureus* (9%), and *Pseudomonas aeruginosa* (8%)[74].

While some cases of post-LP meningitis due to *Staphylococci*, *Pseudomonas*, and other Gram-negative bacilli have been attributed to contaminated instruments or solutions or poor technique[75], studies have suggested that post-LP meningitis could arise from aerosolized oropharyngeal secretions from personnel present during the procedure, especially since many of the causative organisms are found in the mouth and upper airway[76-78].

Based upon these observations, some authors have recommended the routine use of surgical masks during LP and neuroradiologic imaging procedures involving LP[79-81]. Others have questioned the practicality and necessity of the use of those masks since there is no proof that face masks prevent such infections[77-82]. In 2005, the Healthcare Infection Control

Advisory Committee recommended that surgical masks be used by individuals who place a catheter or inject material into the spinal canal, and in 2007 the Centers for Disease Control and Prevention (CDC) endorsed this recommendation[83].

Because meningitis can be caused in animals by performing an LP after first inducing a bacteremia[84, 85], several authors have speculated that an LP in a bacteremic patient without preexisting meningitis might actually cause meningitis[86]. However, this phenomenon is rare, if it occurs at all. In a retrospective study of 1,089 bacteremic infants, the incidence of spontaneous meningitis in children who underwent LP and subsequently developed meningitis was not statistically different from those who did not undergo LP (2.1 versus 0.8%)[87].

An LP through a spinal epidural abscess can result in the spread of bacteria into the subarachnoid space. Since an LP is not needed for diagnosis, the procedure should not be performed in most patients with suspected epidural abscess in the lumbar region[36].

Bleeding

The CSF is normally acellular, although up to five red blood cells (RBCs) are considered normal after LP due to incidental trauma to a capillary or venule. A higher number of RBCs is seen in some patients in whom of the white blood cell (WBC) to RBC ratio and the presence or absence of xanthochromia may differentiate LP-induced from true CNS bleeding.

Serious bleeding that results in spinal cord compromise is rare in the absence of bleeding risk[88]. Patients who have thrombocytopenia or other bleeding disorders or those who received anticoagulant therapy prior to or immediately after undergoing LP have an increased risk of bleeding[42, 89]. A high index of suspicion of spinal hematoma should be maintained in all patients who develop neurologic symptoms after an LP, including those with no known coagulopathy. In rare cases, intraventricular, intracerebral, and subarachnoid hemorrhages have also been reported as complications of LP[90, 91].

In this literature review, no study was found that examined the risk of bleeding following LP based upon the degree of thrombocytopenia or clotting study abnormalities. Due to a lack of data in the literature, it is prudent to not to perform an LP in patients with coagulation defects who are actively bleeding, have severe thrombocytopenia (e.g., platelet counts lower than 50,000/µl), or an international normalized ratio (INR) higher than 1.4, without correcting the underlying abnormalities[92, 93]. When an LP is considered urgent and essential in a patient with an abnormal INR or platelet count whose cause is not obvious, consultation with a hematologist may provide the best advice for safe correction of the coagulopathy prior to performing the LP.

For elective procedures in a patient receiving systemic anticoagulation, observational studies and expert opinion have suggested stopping unfractionated intravenous heparin drips two to four hours, low-molecular-weight heparin 12 to 24 hours, dabigatran one to two days, and warfarin five to seven days prior to spinal anesthesia or LP[94, 95]. The optimal timing of restarting anticoagulation after LP is not known, the incidence of spinal hematoma in the above-mentioned series was much lower when anticoagulation was started at least one hour after the LP[26].

Aspirin and other antiplatelet agents have not been implicated to increase the risk of serious bleeding after LP[96], although studies were not held with clopidogrel, ticlopidine, or a GP IIb/IIIa receptor antagonists. Therefore, it may be reasonable to suspend treatment with thienopyridine derivatives (clopidogrel, ticlopidine) when possible, for one to two weeks prior to an elective LP; for GP IIb/IIIa receptor antagonists, a shorter period of treatment cessation (eight hours for tirofiban and eptifibatide, and 24 to 48 hours for abciximab) may be indicated[97].

Female sex, increased age, a history of excessive bruising/bleeding, hip surgery, continuous catheter anesthetic technique, large needle gauge, multiple needle passes, and moderate or difficult needle placement were all significant risk factors for minor bleeding at the site of catheter placement[97].

Cerebral herniation

The most serious complication of LP is cerebral herniation. Suspected increased intracranial pressure (ICP) is a relative contraindication to perform an LP and also requires independent assessment and treatment. Series of cases estimates that an unfavorable outcome is present in 12%-13% of patients with increased ICP that underwent a LP[98].

The concern about this serious complication has resulted in routine CT scanning prior to LP being the standard of care in many emergency departments[99]. However, this practice delays the performance of LP, and when applied to patients with suspected bacterial meningitis, it could postpone the introduction of treatment or limit the diagnostic power of CSF analysis when performed after antibiotic administration. Moreover, CT scanning is not necessary in all patients prior to LP and may not be adequate to exclude elevated ICP in others[100, 101]. Some studies suggest that high-risk patients can be identified, allowing the majority of patients to safely undergo LP without screening CT[99, 102].

The clinical features commonly associated with increased intracranial pressure are altered mentation, focal neurologic signs, papilledema, seizure within the previous week and/or impaired cellular immunity[99]. A CT scan should not be performed before an LP in patients with suspected bacterial meningitis unless one or more risk factor is present.

Mass lesions causing elevated ICP are usually easily identified on CT scan. However, the CT scan should also be scrutinized for more subtle signs, including diffuse brain swelling as manifested by loss of differentiation between gray and white matter and effacement of sulci, as well as ventricular enlargement and effacement of the basal cisterns[103].

When the LP is delayed or deferred in the setting of suspected bacterial meningitis, it is important to obtain blood cultures (which reveal the pathogen in more than half of patients) and promptly institute empirical antibiotic therapy. Urgent evaluation and treatment of increased intracranial pressure, along with the administration of antibiotics and steroids, should be instituted promptly when this is suspected.

Epidermoid tumor

The formation of an epidermoid spinal cord tumor is a rare complication of LP that may become evident years after the procedure is performed[104-106]. Most reported cases are children aged 5 to 12 years who had a LP in infancy; however, this has also been described in adults[107-109]. It may be caused by epidermoid tissue that is transplanted into the spinal canal during LP without a stylet, or with one that is poorly fitting. This complication can probably be avoided by using spinal needles with tight-fitting stylets during LP[110, 111].

Abducens palsy

Both unilateral and bilateral abducens palsy are reported complications of LP[112-114]. They are believed to result from intracranial hypotension and are generally accompanied by other clinical features of post LP headache. Most patients recover completely within days to weeks. Other cranial nerve palsies are rarely reported[115].

Radicular symptoms and low back pain

It is not uncommon (13% in one series) for patients to experience transient electrical-type pain in one leg during the procedure[116]. However, more sustained radicular symptoms and radicular injury appear to be rare[117]. Up to one-third of patients complain of localized back pain after LP; this may persist for several days, but rarely beyond[116].

PERSPECTIVES AND BIOMARKERS

In the latest decade, many potential biochemical indicators of CNS diseases have been studied. A highlight should be given to the recent studies on useful markers of neurodegeneration, such as amyloid β-peptides (Aβ42 and Aβ40), neurofilament light (Nfl), neurogranin (Ng), total tau (T-tau) and phosphorylated tau (P-tau) CSF levels[118]. These biomarkers are important tools to an early diagnosis and treatment of cognitive decline in Alzheimer disease[119, 120], chronic traumatic encephalopathy[121] and frontotemporal dementia[122], among other neurocognitive disorders.

A large case-control study published in 2018 established an algorithm based on CSF biomarkers to aid with differential diagnosis between the two most common types of dementia: frontotemporal lobar degeneration (FTLD) and FTLD associated with Alzheimer disease (AD). The authors propose a two-step algorithm based on CSF levels of P-tau and Aβ42, where a high P-tau to Aβ42 ratio would indicate FTLD with comorbid AD and low P-tau to Aβ42 ratio would indicate a ''pure FTLD''. Within this last group, a high P-tau level is associated with the Tau subtype of FTLD and a low P-tau level is related with the TDP subtype[122].

The identification of infectious causes of meningitis has also improved, notably for the diagnosis of microorganisms that are difficult to culture or isolate. Recent studies have shown that metagenomic next-generation sequencing (mNGS) of CSF or brain tissue screens for nearly all potential CNS infections and can identify novel or unexpected pathogens in chronic or subacute meningitis[123, 124].

Likewise, researches on CSF biomarkers for psychiatric disorders have been held in the past few years, such as reduced levels of soluble superoxide dismutase-1 (SOD1) in patients with early onset schizophrenia[125] and high levels of isocitrate dehydrogenase in bipolar disorder, suggesting that it could be a trait biomarker of the disease[126].

CONCLUSION

The development of the LP as a routine clinical procedure for obtaining CSF facilitated rapid growth in the formal examination of this fluid. Ever since it has begun, CSF analysis

has played an important role in the identification of multiple neurological conditions, such as infections of the CNS, inflammatory and demyelinating diseases and subarachnoid hemorrhage. Analytical techniques progressed substantially in the past decades, and the discovery of new biomarkers is promising for the advance of diagnostic tools for CNS diseases. Researches should continue in this field to allow further development of current technologies.

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CORRESPONDING AUTHOR

João Paulo Santiago de Oliveira ID 0000-0001-6555-3480
e-mail: jpsoliveira91@gmail.com