J Neurol
DOI 10.1007/s00415-012-6413-x

REVIEW

Cerebrospinal fluid and lumbar puncture: a practical review

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Received: 11 October 2011 / Revised: 19 December 2011 / Accepted: 5 January 2012

Abstract Cerebrospinal fluid is vital for normal brain function. Changes to the composition, flow, or pressure can cause a variety of neurological symptoms and signs. Equally, disorders of nervous tissue may alter cerebrospinal fluid characteristics. Analysis of cerebrospinal fluid can provide information on diagnosis, may be therapeutic in certain conditions, and allows a research opportunity into neurological disease. However, inappropriate sampling, inaccurate technique, and incomplete analysis can contribute to significant patient morbidity, and reduce the amount of accurate information obtained. In this article, we will review how cerebrospinal fluid is produced, circulated, and resorbed. We will also review lumbar puncture technique, equipment, and cerebrospinal fluid analysis. We also discuss how to minimize the risks and address the complications associated with lumbar puncture.

Keywords Cerebrospinal fluid · Analysis · Lumbar puncture · Technique · Complications

Introduction

Cerebrospinal fluid (CSF) has an essential role in normal brain function, and variation in its constituents, flow, and pressure can negatively impact normal brain function. Equally, abnormal brain function can affect the CSF, so collection and analysis of CSF can therefore provide important information to aid neurological diagnosis. In this paper, we will discuss CSF production, circulation, drainage, and pressure. We will also discuss how CSF should be sampled, explain the potential risks, and ways to minimize or manage these risks.

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Intracranial pressure

Intracranial pressure (ICP) is dependent on CSF dynamics and cerebral blood circulating pressure. ICP in turn influences the cerebral perfusion pressure (CPP) as shown by the equation:

$$\text{CPP} = \text{mean arterial blood pressure} - \text{ICP}$$

CPP controls cerebral blood flow [1], a vital determinant of viable brain tissue. As fragile brain tissue is enclosed in a rigid cranium, relatively small changes in either CSF pressure or cerebral blood volume can significantly alter the ICP. In turn, fluctuations in ICP can have dramatic effects on cerebral blood volume through compression of the venous sinuses and reduction in venous blood flow. Significantly impaired venous blood flow may contribute to venous infarction and loss of brain function. Numerous pathological and physiological processes, e.g., space-occupying lesions, obstructed CSF flow, and jugular vein compression, can impair ICP homeostasis and result in either locally or globally impaired cerebral blood flow with potential implications for brain function.

CSF dynamics

CSF dynamics are dependent on the balance between CSF production and drainage. CSF occupies the ventricular

Published online: 26 January 2012

system along with the cranial and spinal subarachnoid spaces that lie between the arachnoid and pia mater. CSF has two main functions:

1. The fluid submerges the brain, reducing the effective weight of the brain from 1,500 to around 50 g, acting as a 'shock absorber' to prevent the brain from being damaged by mechanical injury.
2. To provide a medium for the transfer of nutrients and waste products to and from the brain tissue.

In normal adults, the volume of CSF is between 125 and 150 ml, of which approximately 20% is contained within the ventricles. Eighty percent of the CSF is produced in the lateral, third, and fourth ventricles by the choroid plexus (CP) [2] with a smaller volume being produced by the ventricular ependyma, arachnoidal membrane, and brain tissue itself [3, 4].

The dynamic circulation of CSF is driven by the secretion of CSF from the CP at the rate of approximately 25 ml/h [5]. This constant flow of CSF displaces the old fluid, thus ensuring a stable environment within the brain and assisting in the removal of waste products. The CP is one of the most efficient secretory tissues in the body [6]. Macroscopically, the CP is a branched structure of microvilli. Each villus is composed of a core of connective tissue and fenestrated capillaries surrounded by an epithelial monolayer. The epithelial cells are joined by tight junctions at their apical surface; this arrangement forms the blood–CSF barrier (Fig. 1).

CSF secretion

The initial step in CSF secretion is likely to be passive due to ultrafiltration of plasma from the leaky, fenestrated capillary network into the connective tissue stroma of the CP. Thereafter, CSF secretion is thought to be predominantly an active process, involving multiple ion channels on both the basal and apical surfaces of the CP epithelium. Sodium ions are transported from the CP connective tissue across the CP epithelial cell and into the ventricular space

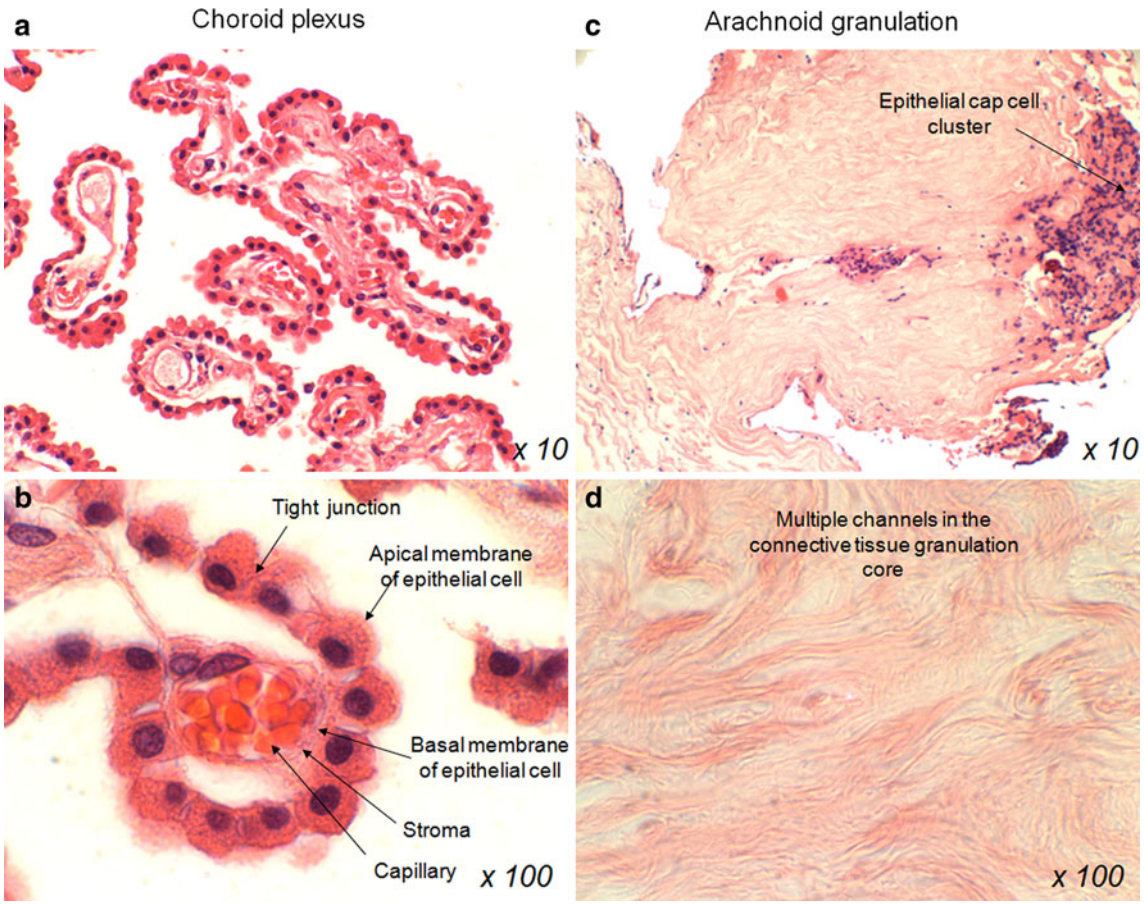

Fig. 1 Hematoxylin and eosin (H&E) staining. The choroid plexus (CP) composed of a single layer of epithelial cells surrounding an abundant capillary network and stromal cells. The villus projects into the cerebrospinal fluid-filled ventricle (**a** and **b**). The arachnoid granulation (AG) composed of the epithelial cap cells covering the core of connective tissue which forms channels for CSF flow (**c** and **d**)

containing CSF. This creates an osmotic gradient, which pulls water into the ventricles. This process is analogous to fluid secretion in other epithelia, e.g., saliva and sweat secretion [6]. Central to this process is the Na^+ K^+ ATPase transporter, located exclusively on the apical surface of the CP epithelial cell [7]. The importance of this transporter is highlighted by the finding that ventricular application of a Na^+ K^+ ATPase inhibitor (oubaine) completely abolishes sodium influx and CSF secretion [2, 8, 9]. There is considerable interplay between numerous other ion transporters in the CP epithelial cells. The effects of these other ion transporters on CSF secretion are illustrated by the ability of inhibitors to reduce CSF secretion. CSF secretion is impaired by bumetanide, via its actions on the Na^+ K^+ $2Cl^-$ co transporter [10], furosemide, due to inhibition of the K^+ Cl^- co transporter [11] and amiloride, due to inhibition of the basal Na^+/H^+ exchanger [12], which is thought to control sodium entry into the epithelial cell. In addition, chloride secretion is blocked by 4,4′-diisothiocyanatostilbene-2,2′-disulphonic acid at the Cl-/HCO3- transporter in the CP [13].

Aquaporins, small hydrophobic integral membrane proteins with the primary function of facilitating water transport, are also thought to have a role in CSF secretion [6]. Within the CP, aquaporin 1 and 4 have been identified in rat models [14, 15], although the contribution of aquaporin channels to CSF production has not been studied.

Carbonic anhydrase, an enzyme that catalyses the reversible hydration of carbon dioxide, also has a role in CSF secretion. Twelve isoforms of carbonic anhydrase have been identified, with both carbonic anhydrase II and III being identified in the CP [16–19]. Acetazolamide, a carbonic anhydrase inhibitor, reduces CSF secretion in rats by 50% [20], supporting the importance of this enzyme in CSF secretion. Acetazolamide does not inhibit carbonic anhydrase III, potentially explaining why it is only partially effective in inhibiting CSF secretion.

CSF circulation

CSF produced in the lateral ventricles flows through the intraventricular foramina (foramina of Monro) into the third ventricle and then to the fourth ventricle via the cerebral aqueduct. CSF drains from the fourth ventricle via the foramina of Luschka and the foramen of Magendie into the subarachnoid space. The foramina of Luschka (lateral apertures) are located in each of the lateral recesses of the fourth ventricle and the foramen of Magendie (median aperture) is located medially to the fourth, both of these apertures permit the drainage of CSF from the fourth ventricle into the subarachnoid space near the pontine cistern (Fig. 2).

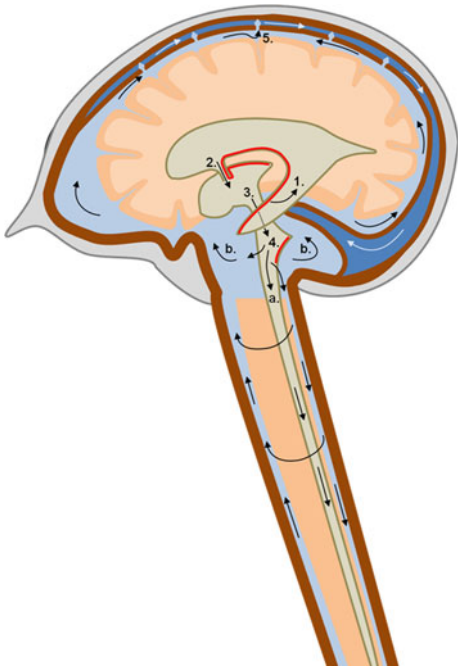

Fig. 2 Schematic diagram of CSF flow. *1* CSF produced by the CP (*red*). *2* CSF moves from lateral ventricle to the 3rd ventricle via the interventricular foramen. *3* CSF moves from 3rd ventricle to 4th ventricle via the cerebral aqueduct. *4* From the 4th ventricle CSF can either: *a* continue within the ventricular system and flow through the spinal canal or, *b* flows into the subarachnoid space via the foramen of Magendie (*located medially*) or via the foramina of Luschka (*located laterally*). *5* The CSF that flows into the subarachnoid space (cranial and spinal) is reabsorbed into the systemic circulation via the arachnoid villi into the dural-venous sinuses

CSF drainage

CSF drains predominantly via the arachnoid granulation tissue (AGT) into the venous circulation. Each arachnoid villus permits the unidirectional flow of CSF into the systemic blood by acting as a one-way valve. There is evidence that CSF drainage can occur via sites other than the AGT. In 1869, it was suggested that CSF could drain via lymphatic channels [21] and this has since been demonstrated in a number of animal studies [3]. More recently, post-mortem subarachnoid injection of MICROFIL has demonstrated the drainage of CSF via nasal lymphatics in large mammals, and also in one human [22]. The precise pathway by which CSF enters the nasal lymphatics is unclear. In addition, the extent to which extra-arachnoid CSF drainage takes place needs to be established.

After exiting the ventricular system, CSF flows into the subarachnoid cisterns at the base of the brain. Some of the CSF flows into the spinal subarachnoid space. The spinal cord terminates at the level of the first or second lumbar vertebrae, but the subarachnoid space extends rostrally towards the second sacral vertebra. The CSF that occupies

this space, known as the lumbar cistern, can be sampled during a lumbar puncture (LP).

Lumbar puncture

A lumbar puncture (LP) is an invasive technique that accesses the restricted compartment of the subarachnoid space in order to sample CSF. This procedure involves introducing a needle below the termination of the spinal cord, passing through the dura mater of the spinal cord, and permitting access to the subarachnoid space.

LP indications

Quincke described an LP in 1891, being used therapeutically to relieve increased intracranial pressure in children with meningitis. Today, the most common indication for LP is its use as a diagnostic procedure, by obtaining CSF samples for further analysis. The other main indication is therapeutic, either by CSF removal to lower intracranial pressure, or by means of access to the central nervous system (CNS) compartment for drug delivery. Another common reason is for research purposes in studies with appropriate ethical approval.

LP contraindications

LP is contraindicated if the risk of the procedure outweighs the potential benefit. Therefore, this issue arises in cases of diagnostic rather than therapeutic LPs. Specific contraindications are discussed below (summarized in Table 1).

Local infection at site of LP

Needle puncture through infected tissue prior to entry into the arachnoid space could allow infective organisms a direct route of entry into an otherwise sterile compartment. This increases the risk of CNS infection and reduces the diagnostic validity in cases of suspected CNS infection, as positive culture results may represent local tissue infection rather than true CNS infection. Skin lesions at the site of LP, such as psoriatic plaques, increases infection risk.

Uncorrected bleeding diathesis

Thrombocytopenia or an elevated international normalized ratio (INR) increases the risk of hemorrhage and spinal hematoma formation. However, hemorrhage can also occur in the setting of a normal platelet count and INR [23]. To minimize the risk of spinal hematoma, it is recommended that prior to LP the platelet count be above 40×10^9/l, provided that the platelet count is stable, and in the absence of other increased bleeding risks, e.g., coagulopathies, antiplatelet, or anticoagulant medications. To the authors' knowledge, no 'safe' INR has been determined to perform an LP. Locally, an INR of 1.5 or below is deemed acceptable, although this should be reviewed on an individual case basis to determine whether a perceived increased risk of hematoma formation outweighs benefit of the LP procedure. Where possible, drugs that affect coagulation should be discontinued to allow the coagulation profile to normalize to minimize hemorrhagic risks, although the risk of discontinuation and consequent risk of thrombosis needs to be considered [24].

There is no clear evidence that low-dose aspirin given alone increases hemorrhagic risk following LP [25]. It is recommended that thienopyridine derivatives, e.g., clopidogrel and ticlopidine, should be discontinued for 7 and 14 days, respectively [26], although this recommendation is primarily aimed at neuro-radiologists, who may be involved in more invasive spinal procedures, where the risk of hemorrhage may be higher. Discontinuing platelet glycoprotein IIb/IIIa inhibitors for 8 h prior to LP, e.g., tirofiban, has also been suggested [26]. Unfractionated heparin is routinely discontinued for 2–4 h prior to LP. Low-molecular-weight heparin at prophylactic dose is discontinued for 12 h and at therapeutic dose for 24 h to allow normalization of coagulation [26, 27]. Post LP, unfractionated heparin should be delayed by at least 1 h to minimize hematoma risk [28]. We are unaware of any evidence to guide how long after thrombolysis a LP could be conducted. Monitoring fibrinogen levels in this situation may be helpful, but is unproven.

Table 1

Lumbar puncture red flags
Platelet count $<40 \times 10^9$/l
International normalized ratio (INR) >1.5
Local skin infection
Local developmental abnormality, e.g., myelomeningocele
Raised intracranial pressure (with a pressure gradient across the CNS compartments)
CT head recommended
Suspicion of raised intracranial pressure
Age> 60 years
Immunocompromised patient
Previous CNS disease
Recent seizure
Reduced consciousness
Papilloedema
Abnormal neurological examination

CNS central nervous system

Risk of CNS herniation

CNS herniation occurs if there is a change in the pressure gradient within the CNS compartment sufficient to cause movement of CNS tissue out of its normal position. This can involve brain, spinal cord, and nerve root tissue, often with devastating and fatal consequences [29, 30]. In these cases, an abnormal pressure gradient already exists, and it is the further transient lowering of pressure, as a result of CSF withdrawal from an LP, which allows the raised pressure compartment above the LP to move along the pressure gradient and consequently move CNS tissue. This is in contrast to states of uniformly raised intracranial pressure within the whole CNS compartment, e.g., idiopathic intracranial hypertension (IIH), where no internal pressure gradient has developed so is it is safe to perform an LP. Studies have been performed to identify features that may indicate states where a pressure gradient has developed, and therefore guard against performing LP, e.g., an age over 60 years, an immunocompromised patient, previous CNS disease, any recent seizures, reduced consciousness, papilloedema, or an abnormal neurological examination [31, 32]. In these cases, imaging is essential prior to LP. However, in many centers, it is routine practice to perform brain imaging prior to all LPs, even if warning clinical features are not present, particularly as the availability of imaging out of normal working hours has increased. CT imaging is typically utilized, as it is more available than MRI, although it involves radiation exposure. The imaging is obtained to evaluate for features of raised ICP as might occur from mass lesions causing features such as midline shift or effacement of the basal cisterns. It should be emphasized that radiographic appearances should always be put in context of the individual case, and if there is a clinical concern of an internal CSF pressure gradient, then it is important not to be falsely reassured by otherwise normal imaging as imaging findings may be subtle in early stages of disease.

Congenital abnormalities

Developmental abnormalities at the site of LP, e.g., myelomeningocele, may have associated abnormalities of tissue locally, e.g., tethered spinal cord, and therefore this tissue could be traumatized by needle placement as nervous tissue is no longer free to be displaced by needle entry.

LP practicalities

A number of steps should occur to facilitate a successful LP procedure, which are detailed below and summarized in Fig. 3.

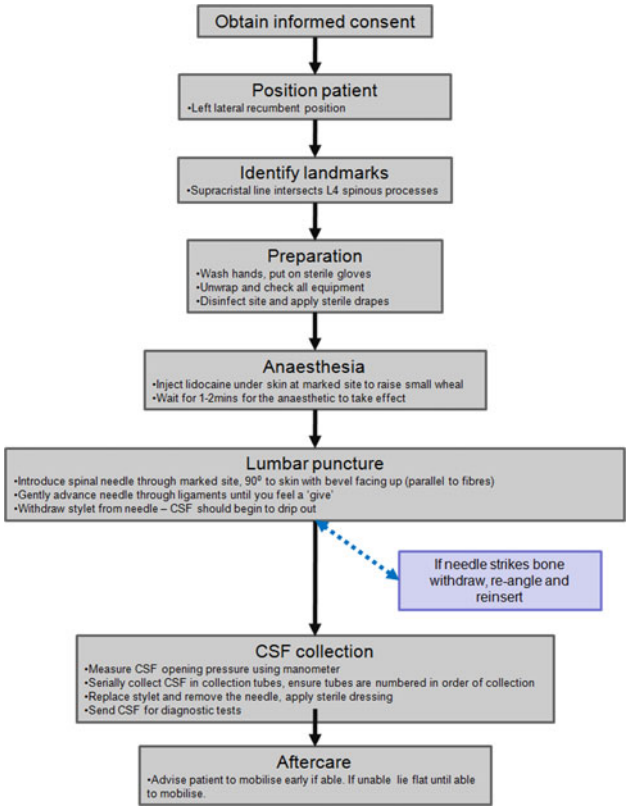

Fig. 3 LP technique summary

Consent

The clinician should obtain consent from the patient and should explain the procedure outlining potential common complications that may arise. These include local discomfort, radicular pain, hemorrhage, infection, and post-LP headache that occasionally necessitates an epidural blood patch if conservative measures fail. While verbal consent is sufficient, it is normal practice to obtain written consent prior to invasive procedures, such as a LP [33]. We typically advise the patient that the needle will be placed below the level of the spinal cord and will not enter the cord. Pain experienced by the patient may be due to the needle coming into contact with exiting spinal nerve roots or bone. We warn the patient that local discomfort, similar to a bruised feeling, at the site of LP site is common after the procedure. We then discuss the risk of complications listed in Table 2.

Equipment

The equipment needed to perform an LP is summarized in Table 3 and shown in Fig. 4a and b. A suitable trolley is cleaned prior to placement of any materials on it. Care should be taken not to contaminate the equipment as the items are opened and placed on a sterile field on the trolley.

Table 2 Complications and associated risks of routine lumbar puncture

Complication	Risk	
Infection	<0.01% [85, 86]	
Bleeding	<0.01% (estimate due to rarity and consequent lack of epidemiology data) [87, 88]	
Post-LP headache	Traumatic needle	Atraumatic needle
	Mean: 26%	Mean: 9%
	(wide range of figures: 9% [89], 14% [87], 24% [90], 32% [91], 32% [92], 36% [93], 36% [94])	(wide range of figures: 3% [93], 3% [89], 6% [92], 12% [90], 19% [91])

Table 3 Equipment required for LP

Equipment
Sterile gloves
Sterile drape
Antiseptic solution, e.g., chlorhexidine
Sterile gauze dressings
5–10 ml 1–2% lidocaine
10-ml syringe
Needles—1× orange (25G) and 2× green (21G)
Lumbar puncture (spinal) needle—length measuring 1.5 in for infants; 2.5 in for children; and 3.5 in for adults
Lumbar puncture manometer (× 2 if elevated pressure suspected)
Three-way tap
3–4 sterile collection tubes
Biochemistry tubes for glucose, and other sample tubes as tests require
Wound dressing or plaster

The three-way tap on the pressure manometer must be opened to allow CSF to flow up the manometer as shown in Fig. 4c.

Patient positioning

There are two positions that the patient can adopt while having an LP:

1. The left lateral recumbent position; (Fig. 4d) where the patient lies on their left-hand side with the neck, knees, and hips flexed as much as possible (may ask patient to clasp their hands around their knees).
2. The sitting position; where the patient sits on the edge of a bed and arches their back (may ask patient to put head between knees or lean over a cushion). This position is not suitable for measuring pressure.

As measuring pressure is part of the routine CSF examination for neurology patients, the left lateral position is preferred, although the sitting position may be used if pressure measurement is not required.

Landmarks

The supracristal line (indicated in Fig. 4d) joins the superior border of the iliac crests. With the patient lying in the lateral recumbent position, this vertical line intersects the spinous process of the L4 vertebra. If a horizontal line is drawn along the tips of the spinous processes of each vertebra, where these lines cross indicates the L4 spinous process. Cranially to this is the L3/L4 interspace, and caudally the L4/L5 interspace, both suitable sites for LP. Other interspaces may also be palpated if necessary by moving along this horizontal line, recognizing that attempts should be made below the termination of the spinal column the vast majority of which end at L1, and others typically by L2-3 if no other spinal malformation is present. A midline approach along this horizontal line will minimize the risk of trauma to the spinal vascular supply. We use a skin marking pen or indentation to mark the position of the interspace.

Preparation

The clinician should wash their hands, put on sterile gloves, and then unwrap and ensure that all equipment is correct. The overlying skin should be cleaned with disinfectant, typically applied in widening concentric circles, and sterile drapes should be applied to the site. An assistant is often helpful in handling non-sterile containers.

Local anesthesia

Draw up 5–10 ml of local anesthetic (lidocaine) in a 10-ml syringe and then discard the needle. With a small needle (orange, 25G or blue, 23G) administer the local anesthetic under the skin to raise a small wheal and wait for the anesthesia to take effect. Topical anesthesia may be applied prior to anesthetic injection if necessary. Confirm that the skin surface has been anesthetized and then replace the needle of the syringe containing the local anesthetic agent with a longer needle (green, 21G) and insert needle through the wheal, and infiltrate approximately 1–2 ml of local

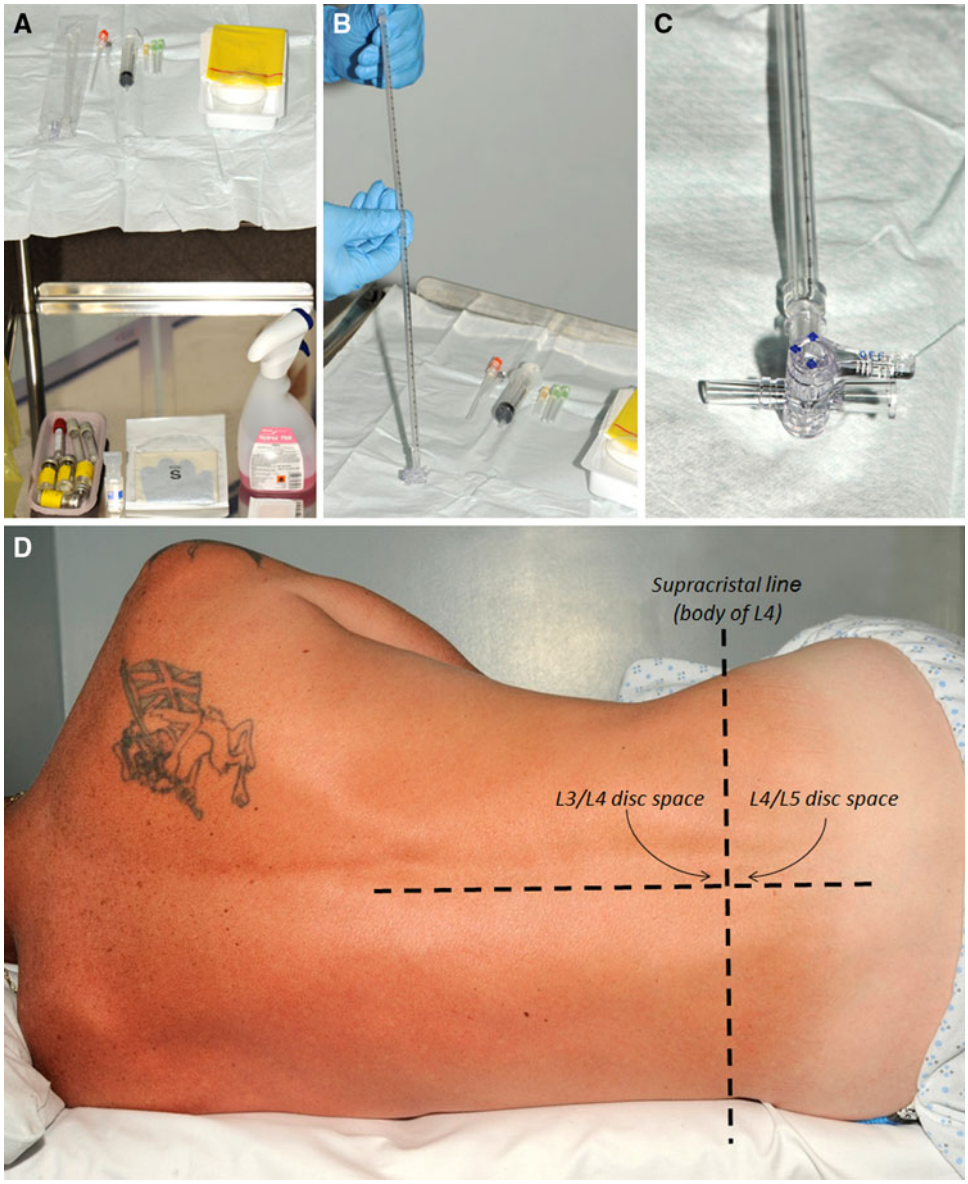

Fig. 4 **a** A cleaned clinical trolley set out for a LP procedure. **b** The manometer is assembled while operating in a sterile field. **c** Close-up photograph of the correct position of the three-way tap so the manometer is set to be used to obtain a CSF pressure reading (thin end to be placed onto spinal needle once CSF access obtained). **d** Patient lying in left lateral position with spinal processes marked by *horizontal dashed line* and supracristal line (L4) marked by *vertical dashed line*. The caudal disc space is that of L3/L4, a suitable site for lumbar puncture

anesthetic, withdrawing the plunger prior to infiltration to ensure no blood vessel is being injected directly. Repeat at 1 to 2-cm intervals as the needle is positioned into deeper tissue layers. Depth of anesthetic infiltration will depend on body habitus. Once completed, withdraw the needle completely and allow time for the anesthetic to take effect, usually 1–2 min.

LP technique

To reduce the risk of headache after an LP, an atraumatic needle is preferred, or, if not available, then a Quincke needle with a small diameter, such as 22G, should be used. If using a Quincke needle, insert with stylet in place, at the superior aspect of the inferior spinous process angling the needle towards the umbilicus. Gently advance the needle through the ligaments. If the needle is positioned in the midline, it should pass through the skin, subcutaneous tissue, supraspinous ligament, interspinous ligament, ligamentum flavum, epidural space, dura, and arachnoid mater into the subarachnoid space. Resistance will be felt as the needle passes through the spinal ligaments and dura, a 'give', will be felt as the needle enters the subarachnoid space. If using an atraumatic needle, the technique is the same, but an introducer is inserted first, with the smaller atraumatic needle then inserted through this (Fig. 5). For either needle type, once in the subarachnoid space, withdraw the stylet within the needle and assess CSF flow. If the attempt is unsuccessful, or the needle strikes bone, withdraw the needle slightly and re-angle the needle and advance in a stepwise fashion until a gap is found. If the patient experiences shooting leg pain, this suggests that the

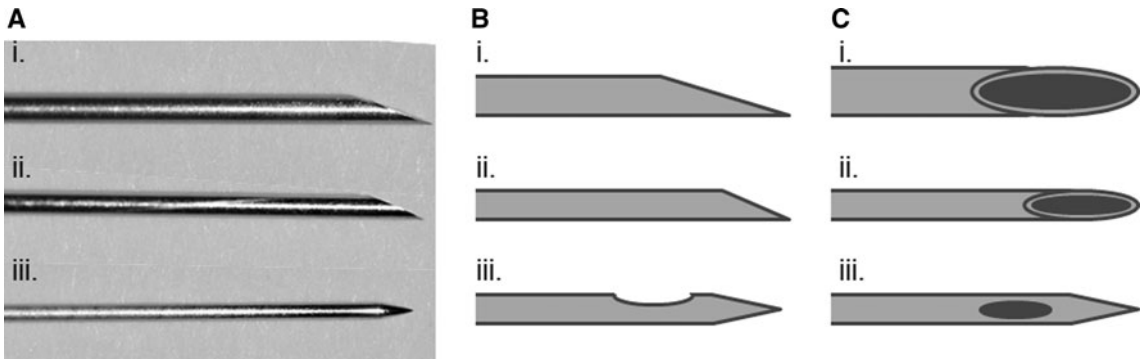

Fig. 5 Photograph (**a**) and schematic representative of lateral (**b**) and superior (**c**) aspects of tips of commonly used spinal needles: *i* yellow Quincke 20G, *ii* black Quincke 22G, *iii* atraumatic 25G. The Quincke needle tips have a sharp cutting bevel, compared to the relatively blunt pencil point of the atraumatic needle, which contains a side port

needle placement is too lateral, and is touching a lateral nerve root. Repositioning the needle and/or the patient is indicated. Try to avoid multiple attempts at different sites during the procedure, as this may cause local swelling and/or bruising and sometimes muscle spasms. This will obscure surface anatomical landmarks, making future attempts technically more difficult. In such cases, prior to further attempts, use of muscle relaxants such as a low-dose benzodiazepine may be helpful.

Longer spinal needles are available to use in very obese patients, although in our experience this can often make the procedure more difficult, as longer spinal needles will typically be more flexible and consequently often divert off course during the procedure. We would therefore recommend using the standard needles where possible and just advancing the needle further into the subcutaneous tissue as required. In a series of 25 obese patients undergoing repeated LPs (body mass index ranging from 27 to 50 kg/m^2), a longer spinal needed was never required [34]. If the LP attempt is completely unsuccessful, despite due care and advice from a colleague experienced in LP technique, ultrasound and X-ray imaging can be used by those experienced in their use to identify appropriate landmarks to facilitate a successful attempt [35].

Throughout the procedure, it is essential to maintain a dialog with the patient, explaining what you are doing at each step. Explanation and compassion will help establish trust between the clinician and the patient to reduce the patient's anxiety.

CSF pressure measurement

Pressure readings are made with the manometer placed over the end of the spinal needle once the stylet has been removed, prior to CSF collection. Manometer readings should be performed with the patient lying in the lateral position. If the dura can only be punctured in the seated position, extreme care is advised in moving the patient to a lateral position, to ensure that the needle is neither displaced nor broken during movement. Pressure recordings in a seated position in an otherwise intracranial hypotensive or normotensive patient are artificially elevated, as the level within the manometer indicates the height of the patient's head from the site of the spinal needle, rather than true ICP. Depending on the caliber of the spinal needle, CSF flow through this and up the manometer may take several minutes to settle. If the level rises above the height of the manometer, additional manometer tubes can be connected until the elevation terminates. To ensure peak pressure has been reached, the patient is asked to inspire and expire several times and the CSF level should oscillate slightly within the manometer, but not increase further, this may take a few minutes. Accurate pressure recordings should be taken when the patient is breathing quietly in a calm state, as Valsalva maneuvers from shouting, crying, or coughing can cause a transient rise in CSF pressure, presumably due to a transient increase in cerebral venous blood pressure [36, 37]. During the pressure reading, the patient's legs should also be straightened slightly at the hips to avoid compression of the intra-abdominal cavity, which could artificially elevate CSF pressure through transmission of raised pressure within the intra-thoracic cavity and consequently increase cerebral venous blood pressure and elevate CSF pressure.

Normal CSF pressure and effects of obesity

Pressure is normally between 10 and 20 cm in adults and the elderly, with levels above 25 cm regarded as being pathological [38–40]. However, in children, the normal range of CSF pressure may be elevated to 28 cm [41]. Obesity is positively associated with intracranial hypertension and weight loss is of proven therapeutic benefit in these patients [34]. However, obesity is thought to only have a modest effect on increasing CSF pressure in normal patients, if at all [38, 39, 42]. Whitley published the largest

study to measure both body mass index (BMI) and CSF opening pressure, examining 242 adult patients undergoing their first lumbar puncture within the same neurological unit for conditions unrelated to CSF pressure disorders [39]. The majority of patients in their sample population were slightly overweight, median BMI 26 kg/m^2. A significant correlation was found between BMI and CSF opening pressure. Patients with normal BMI (18.5–24.9 kg/m^2) had a median CSF opening pressure of 15 cm. In the obese (BMI >30 kg/m^2), median CSF opening pressure was 20 cm. However, as the confidence limits of these median values overlapped considerably, the true figure may not be as great as this, and the authors concluded that the difference was not clinically significant [39].

Alternative techniques to measure CSF pressure

If more continuous pressure recordings are necessary, for example in assessing whether a headache syndrome is associated with a change in intracranial pressure, direct monitoring may be achieved by elective insertion of a pressure bolt. This enters the cranium to enter the epidermal, subarachnoid, or ventricular space and sequential recordings can then be made in the recumbent and supine positions while correlating with patients' symptoms. This is an invasive procedure with associated risks of general anesthesia, hemorrhage, and infection. Depending on the system used, a ventricular site may block the production of an inaccurate record, and alternative non-ventricular sites may be unduly influenced by local tissue irregularities, which also produce inaccurate recordings. In more continuous monitoring, typically used in patients who have had traumatic brain injury, certain types of pressure variations termed, 'waves', have been identified. 'A' waves rise steeply from normal ICP to 50 mmHg or more for 5–20 min before falling again to the same or lower level, indicating reduced CNS pressure compliance. 'B' waves are rhythmic oscillations sharply peaked and occurring once every 1–2 min, where the ICP rises 20–30 mmHg above baseline then falling abruptly, and may be indicative of reduced CNS pressure compliance. 'C' waves are rhythmic oscillations up to 20 mmHg with a frequency of 4–8/min, synchronous with Traube–Hering–Mayer blood pressure variations. For a detailed review of these areas, see Dunn L. T. 2002 [43].

Other techniques to measure pressure include CSF infusion studies where two spinal needles are placed, or one needle if a pressure bolt is sited [44, 45]. Fluid may then be inserted through one site and a pressure recording made at the other to assess resistance to CSF absorption by the arachnoid villi. This procedure may be useful in the diagnosis of normal-pressure hydrocephalus.

Non-invasive measures of CSF pressure have never been sufficiently accurate to warrant their use in the clinical or research environment (e.g., ophthalmodynamometers) [46]. However, ultrasonographic measurement of optic nerve sheath diameter has been shown to be useful as a surrogate measure of raised ICP. As the optic nerve sheath contains the optic nerve, which is surrounded by CSF, as CSF pressure rises, the sheath dilates. Ultrasound measures of the distended of the optic nerve sheath have been used as a quantitative measure of papilloedema in idiopathic intracranial hypertension studies [34].

CSF pressure variability

As previously discussed, transient elevation in CSF pressure may be seen during Valsalva maneuver, shouting, crying, and potentially resulting from abdominal compression from an extreme flexed leg position during LP.

CSF pressure is also known to vary with posture, being highest when lying, falling quickly on sitting and then rising slowly if remaining in that position, although not to the extent noted when lying [47]. Diurnal fluctuation in intracranial pressures is also noted with the highest pressure recordings being observed at night [48]. The time of day and position of the patient must therefore be taken into account when evaluating the intracranial pressure in order for the pressure reading to be reliable (Table 4).

CSF collection

CSF will flow as soon as the stylet has been withdrawn and if the needle has entered the subarachnoid space. If a manometer is in place, the manometer 3 way-tap should be moved so the off position is pointing up the manometer tube to allow free drainage for further sample collection. If the LP is traumatic, the CSF samples will be tinged with blood, which should disappear with serial collections. CSF will drip into the collecting tubes and should not be aspirated, as slight negative pressure may increase the risk of herniation. There is no standard amount of CSF that should be removed during an LP. The minimal amount of CSF required for an investigation should be collected. However, there is much variation depending on the purpose of the LP, ranging from as little as 0.5 ml for analysis of glucose, proteins, and antigen, 0.1 ml for oligoclonal bands, and up to 20 ml for mycobacterial or fungal culture. It is good practice to fill 3–4 collecting tubes with at least 5 ml of CSF each. The amount of CSF removed is unlikely to impact the rate of post-dural puncture headache, as CSF is produced at a rate of 25 ml/h and so the collected sample is rapidly replaced. Caution is, however, advised in elderly patients with very atrophic brains, as subdural bleeds can result if excessive amounts of CSF are removed, due to slumping of the brain towards the foramen magnum as the

Table 4 Differential diagnosis of neurological disease according to intracranial pressure

	Hypotension	Normotension	Hypertension
Primary	CSF leak	Normal pressure hydrocephalus	Idiopathic intracranial hypertension
	Atraumatic/ spontaneous	CNS demyelination	Intracranial hypertension without papilloedema (IWOP)
		Beçhet's syndrome	
		CNS vasculitis	
		Neuropathy	
Secondary	CSF leak	Encephalitis	Intracranial space-occupying lesion[a]
	Post LP		Choroid plexus papilloma
	Post surgical		Arachnoid granulation agenesis
	Trauma		Hydrocephalus (communicating and non-communicating)
	Post-coital		Infective meningitis
	Drugs		Acute bacterial
	Acetazolamide		Cryptococcal
	Bendroflumethiazide		Tuberculosis
	Furosemide		Viral[a]
	Indometacin		Fungal[a]
	Topiramate[b]		Cerebral venous sinus thrombosis
			Acute hemorrhagic leucoencephalitis
			Neurosarcoidosis[a]
			Guillian-Barré syndrome[a]
			Malignant meningitis[a]

CNS indicates central nervous system

[a] may also be normal pressure

[b] may have indirect effect through weight loss

CSF is removed with consequent traction and damage to small supporting subdural blood vessels.

CSF analysis

Subarachnoid hemorrhage

The first and third bottles are typically sent for microscopy to assist in the identification of subarachnoid hemorrhage as the number of red blood cells will not reduce between the samples in the case of subarachnoid hemorrhage but will if they have resulted from a traumatic, 'bloody', tap. Definitive testing for subarachnoid blood is performed by assessing for the presence of xanthochromia, an orange–yellow pigment formed by the combination of oxyhemoglobin and bilirubin. Oxyhemoglobin is formed from the breakdown of red blood cells but levels can be overrepresented due to a traumatic CSF tap. Additionally, agitation, as might occur during handling and transport, will also facilitate the breakdown of red blood cells and may falsely elevate oxyhemoglobin levels. The haem component of the red blood cell is converted to bilirubin, approximately 9–15 h later. Bilirubin levels but may be degraded if the sample is exposed to ultraviolet light, but can also be falsely elevate in cases of raised serum bilirubin [49]. Red blood cell metabolites are eventually broken down, but may be identified in the CSF up to 14 days after the presumed hemorrhage [50]. Correct CSF analysis for xanthochromia is therefore enhanced by:

- Normal serum bilirubin levels.
- Delaying CSF sampling until the red cells have broken down to bilirubin (12-h post-event is recommended).
- Using the least blood-stained CSF sample, usually the last CSF sample collected.
- Transporting the CSF sample in the dark with minimal agitation.
- Analyzing the sample with spectrophotometry rather than visual inspection.

Microscopy, biochemistry, and virology

Microscopy calculates the number of white cells in the CSF sample. Excessive numbers of red blood cells, as might arise from a traumatic tap, can artificially elevate the white cell level, and it is regarded that for every 1,000 red blood cells, the white cell count is elevated by 1. Therefore, a calculation should be performed to account for this when necessary. If viral meningitis is suspected, viral polymerase chain reaction (PCR) assessment for herpes 1 and 2, *Varicella zoster*, and enterovirsuses is also completed. Other

investigations for infectious organisms can be performed if indicated, e.g., fungal infections such as *Cryptococcus* and *Histoplasma* as well as other pathogens such as Lyme disease, Whipple's disease, syphilis, measles, and the John Cunningham virus (JCV). In cases of suspected tuberculosis (TB), several tests may be performed. Smear for presence of acid-fast bacilli has a low sensitivity and is non-specific. PCR for TB is more specific but also has a low sensitivity. Specific successful culture for *Mycobacterium tuberculosis* can take 4–12 weeks. In cases where a wide differential diagnosis exists, an extra CSF sample may be usefully collected and stored in case further CSF tests are later required, e.g., in proven cases of CSF lymphocytosis in patients with suspected viral encephalitis additional virology polymerase chain analysis can then be requested.

The second collection bottle is tested by the biochemistry department for protein and an additional fluoride sample bottle is tested for glucose. Here it is important to send a paired serum glucose sample to enable comparison of serum and CSF glucose (e.g., pathologically low glucose exists if the CSF level is less than half the serum glucose level). In pediatrics, a low CSF glucose without other CSF abnormality should prompt consideration of glucose transporter-1 deficiency, a genetic condition that causes a syndrome of epilepsy, movement disorders, and developmental delay. The interpretation of the routine microbiology and biochemistry results are summarized in Table 5.

Lactate

In pediatrics where diseases arising from inborn errors of metabolism are suspected, CSF lactate and/or glycine are calculated, although abnormal levels may not be specific for these conditions [51, 52]. CSF lactate may also be used to investigate mitochondrial CNS disease [53]. There is an expanding phenotype of pediatric disorders resulting from impaired CNS neurotransmitter metabolism, and diagnosis of these requires careful collection and analysis of these and their breakdown products for accurate diagnosis [54].

CSF immunology

CSF may be sent to the immunology department for oligoclonal band analysis. These are proteins, principally gamma immunoglobulin, thought to represent a local B cell immune response, but may represent systemic infection or systemic immunoglobulin production, e.g., myeloma. Therefore, a paired serum sample needs to be sent with the CSF sample to identify cases where bands are identified within the CSF only, and may then indicate an abnormal B-cell CNS immune response [55]. Therefore, while typically used to assist in the identification of immune-mediated CNS disorders, principally multiple sclerosis [56], isolated CSF bands may also be present in paraneoplastic disorders [57], systemic lupus erythematosus [58], neurosarcoidosis [59], cerebral angiitis [60], and CNS infections [55], but is usually absent in neuro-Behçet's [61].

CSF antibodies may also be helpful in diagnosing autoimmune conditions, e.g., aquaporin-4/anti-neuromyelitis optica antibody for Devic's disease, anti-glutamic acid decarboxylaseantibodies for stiff person syndrome, or anti-*N*-methyl D-aspartate (NMDA) antibody for anti-NMDA-mediated encephalitis. As the knowledge about autoimmune CNS conditions grows, it is inevitable that the number of different immune complexes that can be tested will increase. CSF cytokine composition can also sometimes be useful to monitor response to treatment, e.g., interleukin-6 in neurosarcoidosis in response to infliximab, but this is not routine practice.

CSF histology

In cases where CNS malignancy is considered (e.g., carcinomatous meningitis and lymphoma), a sample should be sent to histology for analysis. Ideally, the sample needs to be prepared on a histology slide within 2 h of being collected, as cells within the CSF will lyse very rapidly,

Table 5 Routine CSF constituents in different CNS disorders

	Normal	Viral infection	Bacterial infection	Fungal infection	TB infection	GBS and spinal shock	Multiple sclerosis
Appearance	Clear	Clear/ opaque	Turbid	Clear	Clear/opaque	Clear	Clear
White cells (per mm^3)	0–5	10–2,000	100–60,000	20–500	50–5,000	Normal	>15 atypical (>50 very rare)
Protein (g/l)	<0.5[a]	0.5–0.9	>0.9 (1.0–5.0)	>0.5 (0.5–5.0)	>1.0 (1–5)	>1.0	Normal
Glucose (% serum glucose)	>60–75% (2.2–4.4 mmol/l)	Normal	<40%	<80%	<50%	Normal	Normal

[a] Reference range can vary between laboratories. Adapted from Clarke et al. [95]

reducing the utility of the examination. The sensitivity is increased by sending a number (e.g., three) of large volume (5–10 ml) samples from sequential lumbar punctures [62]. The specimen will be centrifuged in the laboratory and after preparing on a slide, the cell morphology will be reviewed. A predominantly monoclonal expansion of large lymphocytes would suggest a primary B cell lymphoma. A heterologous population, composed of mostly T cells and a few B cells, is more likely to reflect reactive changes within the CSF. Immunocytochemistry may also be conducted to further evaluate for specific cell surface markers.

Other

CSF protein 14-3-3 is used as a biomarker of rapid neurodegeneration typically seen in classic Creutzfeldt-Jakob disease, and together with S-100β as a marker of gliosis, are used alongside other investigations to increase the sensitivity of this diagnosis. Low CSF hypocretin is associated with narcolepsy. The utility of CSF angiotensin-converting enzyme (ACE) levels, as a test for neurosarcoidosis, has lost favor, being neither sensitive nor specific, although serum ACE levels might be of value [63]. CSF leaks giving rise to CSF rhinorrhoea or otorrhoea may also be differentiated from other types of fluid, by opportunistic collection and subsequent analysis for tau protein [64].

Future CSF tests

In the future, other CSF tests currently being developed in a research capacity are likely to become more routine in clinical practice as either an additional diagnostic test or as biomarkers in chronic neurological conditions, e.g., CSF tau and Aβ42 in Alzheimer's disease and metabolomic profiles [65].

Complications

Local discomfort and radicular pain

Discomfort at the site of needle entry is common post-procedure, and minimized by using small bore or atraumatic needles with a single successful attempt. Pain or backache should settle promptly, with more severe or persistent pain necessitating further investigation for possibility of hematoma formation (see below). Radicular pain during the procedure suggests that the needle is too lateral, and repositioning is required. Persistent radicular pain is rare.

Spinal hematoma

Spinal hematoma can cause spinal cord or cauda equina compression, and 37% of cases will remain permanent paraplegic [23, 28]. A spinal hematoma may not be clinically obvious. The clinician should be alerted to this possibility if the patient develops post-LP severe, persistent back pain, or radicular pain (58% of cases), new sensory or motor symptoms, sphincter disturbance, or meningism [23]. Hematomas will typically present in the first 6 h following the LP (58% of cases), although 22% will present greater than 24 h after the procedure [23]. Prompt magnetic resonance scanning should be performed if suspicion of hematoma arises, as a delay in diagnosis has been associated with a poor prognosis [66]. Management of spinal hematomas should be in liaison with neurosurgical colleagues. Conservative management may be possible, particularly if symptoms are mild and there are early signs of neurological recovery [23]. In these cases, prolonged monitoring is necessary, as patients may have a delayed deterioration. Dexamethasone may also be useful, 4 mg four times per day for 48 h, although there is no evidence to support this. In more severe cases, or where the patient is deteriorating, surgical evacuation of the hematoma may be required.

Meningitis

Meningitis is a rare complication of LP. Patients may present as is seen in other causes of meningitis, headache, meningism, photophobia, neck stiffness, and be pyrexic. These typical features may be masked in immunocompromised patients. Appropriate antimicrobial therapy will depend on local hospital guidelines and should be discussed with the microbiologists, but typically involve a third-generation cephalosporin.

Post-LP headache

Headache following an LP is common (see Table 2). The headache syndrome is caused by a low-pressure (intracranial hypotension) phenomenon, resulting in postural, orthostatic, worsening within 15 min of elevation of the head into either a sitting or standing position, and improves within 15 min of lying down. The headache is also associated with at least one of the following: neck stiffness, tinnitus, hyperacusis, photophobia, or nausea. In addition, the headache will characteristically occur within 5 days of dural puncture and typically resolves within 1 week of conservative management, or within 48 h of definitive treatment, usually an epidural blood patch [67]. The headache syndrome itself varies in location, but is typically occipital or holocranial, dull in character, and worsens with Valsalva maneuvers.

Most low-pressure headaches will resolve rapidly as CSF is produced at a rate of approximately 25 ml/h. Patients have traditionally been asked to lie flat following

an LP to mitigate the chance of developing a low-pressure headache. However, there is no evidence to suggest a benefit of this approach [68–71]. Our practice following an LP is to advise the patient to lie flat until they feel well, as some patients may experience syncopal symptoms if they mobilize too rapidly, and then to mobilize as they feel able.

Rarely, post-LP headache can be caused by intracranial subdural hematoma [72]. Symptoms suggestive of this include prolonged, prominent headache without postural features, reduced consciousness, and focal neurological signs. Contributing factors include pregnancy, multiple punctures, use of anticoagulants, intracranial vascular abnormalities, and brain atrophy [73].

The more common reason to produce intracranial hypotension post LP is that the dural puncture site has not sealed on withdrawal of the needle. To prevent this, atraumatic needles, which have a pencil point tip rather than a cutting edge, are advocated (Fig. 5). Atraumatic needles are more expensive (£8.98) compared to Quincke 22G (£3.72) and Quincke 20G (£1.23). However, they are associated with a reduced risk of post-LP headache (for review see Arendt K et al. [74]), and therefore minimize the risk of delayed hospital discharge and/or readmission. Rates of post-LP headache are further reduced when using the atraumatic needle, if the needle stylet is reintroduced prior to withdrawal of the needle [75].

Persistent CSF leak following LP

In patients who do not have intracranial hypertension, a persistent leak at a rate that is the same or more than the rate of CSF production will produce intracranial hypotension, and persistence of the low-pressure headache beyond the first hour. Symptoms are alleviated by bed rest, but simple analgesics may be used when the patient needs to mobilize. There is no role for fluid supplementation [76]. However, caffeinated drinks, or caffeine orally as 300 mg [77], or occasionally intravenously (500 mg in 500 ml normal saline over 2 h with cardiac monitoring is advised, due to potential development of cardiac arrhythmias), is thought to be beneficial through its effect of cerebral vasoconstriction. The patient should be nursed lying flat or with a slight downward head-tilt if tolerated. Conservative measures are successful in the majority of patients but may require 7–10 days to be effective.

Epidural blood patch

An evidence base to determine the most appropriate timing for an epidural blood patch is lacking; however, we suggest that this procedure should be conducted when conservative measures fail, or if symptoms are very disabling. In this procedure, the patient is prepared in the same way as a LP [78]. An anesthetist skilled in epidural needle placement will typically conduct the procedure, which involves injecting 15 ml of the patient's own blood into the epidural space at the level of the original LP. Advancing the needle though the dura should be avoided, as this additional dural puncture may prolong the intracranial hypotension syndrome. Patients are asked to lie with a slight downward head-tilt to assist tracking of the blood within the epidural space to tamponade the CSF leak. Symptoms typically improve dramatically within just a few hours. The blood patch may be effective due to simply sealing the dural puncture site, however, the blood patch may also cause a local increase in pressure within the epidural space, which is then transmitted through the dura to elevating ICP. It is recommended that patients lie recumbent for at least 2 h before mobilizing, presumably to avoid movement of the epidural blood [79]. If symptoms do not improve within 2 days, it is likely that the procedure has failed, either from using the wrong location, incomplete tracking of the blood within the epidural space to the puncture site, or from creation of a further dural puncture. In such cases, MRI imaging of the spine is advised to ensure that the correct CSF leak site has been identified, although blood product within the epidural space may potentially confound whether there is a CSF collection outside the dural cavity. If further conservative measures including caffeine are unsuccessful then further epidural blood patches may be necessary. Epidural blood patches have a high success rate of over 90%, falling to 61–75% if the initial puncture involved a large bore spinal needle. For a detailed review, see Duffy and Crosby [80]. If a second epidural patch is required, the success rate remains high (>90%) [81].

Therapeutic CSF drainage

Idiopathic intracranial hypertension

A minor CSF leak can be of modest therapeutic benefit in patients with an initial raised CSF pressure (intracranial hypertension) headache syndrome such as IIH as the leak may promote temporary intracranial normotension. In keeping with this, most patients with IIH will experience a temporary remission of their headaches and visual obscurations following an LP. This is a useful diagnostic clue and is worth enquiring about in patients in whom this diagnosis is considered. Serial LPs were used in the past to treat IIH. This is no longer appropriate due to the risks of the procedure and lack of long-term efficacy. Treatment should instead focus on weight loss, a strategy with proven therapeutic efficacy [34]. LP in IIH can, however, be useful to temporarily preserve vision in cases where vision is

rapidly deteriorating, prior to completion of a definitive procedure such as CSF shunting.

Normal-pressure hydrocephalus

CSF drainage can also be useful in diagnosing normal-pressure hydrocephalus (NPH), a syndrome of dementia, urinary incontinence, and gait disturbance characterized normal CSF pressure [82, 83]. Imaging studies demonstrate ventricular enlargement out of proportion to the degree of cerebral atrophy. In cases where the diagnosis is not clear, cognitive tests and distance covered in a timed walk, may be objectively measured before and after LP, where 20–30 ml of CSF have been withdrawn, to look for an improvement which might indicate the therapeutic value of a permanent CSF shunt [84].

Conclusions

Normal CSF constituents and pressure are essential for normal CNS function, continually being replaced in order to achieve optimum conditions for the brain and spinal cord. CNS disorders influence CSF characteristics and consequently analysis of both the CSF pressure and constituents can be highly informative in the diagnostic process. LP can be a daunting prospect for patients, and can have potentially devastating complications. Therefore, a thorough understanding of the technique, together with technical expertise, will ensure that patient discomfort and anxiety are reduced and the potential for complications minimized. All efforts should be made to try to ensure that repeated LPs are not required. A full understanding of why the LP is required will enable, though pre-procedure planning, to ensure that sufficient volumes of CSF are collected with relevant paired serum samples, in the correct containers, with appropriate transport conditions, and that laboratory colleagues are on standby to process urgent samples. LP remains a common diagnostic test, which if performed proficiently, has a low complication rate, a high diagnostic yield, and is usually more tolerable than patients expect.

Conflicts of interest The authors report no conflicts of interest.

References

1. Miller JD, Stanek A, Langfitt TW (1972) Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. Prog Brain Res 35:411–432
2. Welch K (1963) Secretion of cerebrospinal fluid by choroid plexus of the rabbit. Am J Physiol 205:617–624
3. McComb JG (1983) Recent research into the nature of cerebrospinal fluid formation and absorption. J Neurosurg 59(3):369–383
4. Adams JH, Graham DI (1988) An introduction to neuropathology, 2nd edn. Churchill Livingstone, New York, pp 34–36
5. Wright EM (1978) Transport processes in the formation of the cerebrospinal fluid. Rev Physiol Biochem Pharmacol 83:3–34
6. Speake T, Whitwell C, Kajita H, Majid A, Brown PD (2001) Mechanisms of CSF secretion by the choroid plexus. Microsc Res Tech 52(1):49–59
7. Ernst SA, Palacios JR 2nd, Siegel GJ (1986) Immunocytochemical localization of Na^+, K^+-ATPase catalytic polypeptide in mouse choroid plexus. J Histochem Cytochem 34(2):189–195
8. Davson H, Segal MB (1970) The effects of some inhibitors and accelerators of sodium transport on the turnover of 22Na in the cerebrospinal fluid and the brain. J Physiol 209(1):131–153
9. Zeuthen T, Wright EM (1978) An electrogenic NA^+/K^+ pump in the choroid plexus. Biochim Biophys Acta 511(3):517–522
10. Wu Q, Delpire E, Hebert SC, Strange K (1998) Functional demonstration of Na^+-K^+-$2Cl^-$ cotransporter activity in isolated, polarized choroid plexus cells. Am J Physiol 275(6 Pt 1):C1565–C1572
11. Zeuthen T, Wright EM (1981) Epithelial potassium transport: tracer and electrophysiological studies in choroid plexus. J Membr Biol 60(2):105–128
12. Murphy VA, Johanson CE (1989) Alteration of sodium transport by the choroid plexus with amiloride. Biochim Biophys Acta 979(2):187–192
13. Deng QS, Johanson CE (1989) Stilbenes inhibit exchange of chloride between blood, choroid plexus and cerebrospinal fluid. Brain Res 501(1):183–187
14. Nielsen S, Smith BL, Christensen EI, Agre P (1993) Distribution of the aquaporin CHIP in secretory and resorptive epithelia and capillary endothelia. Proc Natl Acad Sci USA 90(15):7275–7279
15. Venero JL, Vizuete ML, Ilundain AA, Machado A, Echevarria M, Cano J (1999) Detailed localization of aquaporin-4 messenger RNA in the CNS: preferential expression in periventricular organs. Neuroscience 94(1):239–250 (pii:S0360-4522(99)00182-7)
16. Halmi P, Parkkila S, Honkaniemi J (2006) Expression of carbonic anhydrases II, IV, VII, VIII and XII in rat brain after kainic acid induced status epilepticus. Neurochem Int 48(1):24–30
17. Masuzawa T, Sato F (1983) The enzyme histochemistry of the choroid plexus. Brain 106(Pt 1):55–99
18. Masuzawa T, Hasegawa T, Nakahara N, Iida K, Sato F (1984) Localization of carbonic anhydrase in the rat choroid plexus epithelial cell. Ann NY Acad Sci 429:405–407
19. Nogradi A, Kelly C, Carter ND (1993) Localization of acetazolamide-resistant carbonic anhydrase III in human and rat choroid plexus by immunocytochemistry and in situ hybridisation. Neurosci Lett 151(2):162–165
20. Vogh BP, Godman DR, Maren TH (1987) Effect of AlCl3 and other acids on cerebrospinal fluid production: a correction. J Pharmacol Exp Ther 243(1):35–39
21. Schwalbe G (1869) Der Arachnoidalraum ein Lymphraum und sein Zusammenhang mit den Perichoriodalraum. Zentralbl Med Wiss 7:465–467
22. Johnston M, Zakharov A, Papaiconomou C, Salmasi G, Armstrong D (2004) Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species. Cerebrospinal Fluid Res 1(1):2
23. Sinclair AJ, Carroll C, Davies B (2009) Cauda equina syndrome following a lumbar puncture. J Clin Neurosci 16(5):714–716. doi: 10.1016/j.jocn.2008.07.079
24. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, Kitchen S, Makris M (2011) Guidelines on oral anticoagulation with warfarin, 4th edn. Br J Haematol 154(3):311–324. doi: 10.1111/j.1365-2141.2011.08753.x

25. Hillemacher T, Bleich S, Wiltfang J, Weber M, Kornhuber J, Frieling H (2006) Should aspirin be discontinued for diagnostic lumbar puncture? J Am Geriatr Soc 54(1):181–182. doi:10.1111/j.1532-5415.2005.00575_12.x
26. Layton KF, Kallmes DF, Horlocker TT (2006) Recommendations for anticoagulated patients undergoing image-guided spinal procedures. AJNR Am J Neuroradiol 27(3):468–470
27. van Veen JJ, Nokes TJ, Makris M (2010) The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopenic individuals. Br J Haematol 148(1):15–25. doi:10.1111/j.1365-2141.2009.07899.x
28. Ruff RL, Dougherty JH Jr (1981) Complications of lumbar puncture followed by anticoagulation. Stroke J Cereb Circ 12(6):879–881
29. Sinniah D, Looi LM, Ortega JA, Siegel SE, Landing B (1982) Cerebellar coning and uncal herniation in childhood acute leukaemia. Lancet 2(8300):702–704
30. Hasegawa K, Yamamoto N (1999) Nerve root herniation secondary to lumbar puncture in the patient with lumbar canal stenosis. A case report. Spine (Phila Pa 1976) 24(9):915–917
31. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ (2001) Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 345(24):1727–1733. doi:10.1056/NEJMoa010399
32. Gopal AK, Whitehouse JD, Simel DL, Corey GR (1999) Cranial computed tomography before lumbar puncture: a prospective clinical evaluation. Arch Intern Med 159(22):2681–2685
33. Beresford HR (1980) Informed consent before lumbar puncture. N Engl J Med 303(26):1534
34. Sinclair A, Burdon M, Ball A, Nightingale N, Good P, Matthews T, Jacks A, Lawden M, Clarke C, Walker E, Tomlinson J, Stewart P, Rauz S (2010) Low-energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ 7:341
35. Stiffler KA, Jwayyed S, Wilber ST, Robinson A (2007) The use of ultrasound to identify pertinent landmarks for lumbar puncture. Am J Emerg Med 25(3):331–334. doi:10.1016/j.ajem.2006.07.010
36. Neville L, Egan RA (2005) Frequency and amplitude of elevation of cerebrospinal fluid resting pressure by the Valsalva maneuver. Can J Ophthalmol 40(6):775–777
37. Greenfield JC Jr, Rembert JC, Tindall GT (1984) Transient changes in cerebral vascular resistance during the Valsalva maneuver in man. Stroke J Cereb Circ 15(1):76–79
38. Corbett JJ, Mehta MP (1983) Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumor cerebri. Neurology 33(10):1386–1388
39. Whiteley W, Al-Shahi R, Warlow CP, Zeidler M, Lueck CJ (2006) CSF opening pressure: reference interval and the effect of body mass index. Neurology 67(9):1690–1691
40. Malm J, Jacobsson J, Birgander R, Eklund A (2011) Reference values for CSF outflow resistance and intracranial pressure in healthy elderly. Neurology 76(10):903–909. doi:10.1212/WNL.0b013e31820f2dd0
41. Avery RA, Shah SS, Licht DJ, Seiden JA, Huh JW, Boswinkel J, Ruppe MD, Chew A, Mistry RD, Liu GT (2010) Reference range for cerebrospinal fluid opening pressure in children. N Engl J Med 363(9):891–893. doi:10.1056/NEJMc1004957
42. Bono F, Lupo MR, Serra P, Cantafio C, Lucisano A, Lavano A, Fera F, Pardatscher K, Quattrone A (2002) Obesity does not induce abnormal CSF pressure in subjects with normal cerebral MR venography. Neurology 59(10):1641–1643
43. Dunn LT (2002) Raised intracranial pressure. J Neurol Neurosurg Psychiatry 73(Suppl 1):i23–i27
44. Katzman R, Hussey F (1970) A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. Neurology 20(6):534–544
45. Eide PK, Brean A (2010) Cerebrospinal fluid pulse pressure amplitude during lumbar infusion in idiopathic normal pressure hydrocephalus can predict response to shunting. Cerebrospinal Fluid Res 7:5. doi:10.1186/1743-8454-7-5
46. Jonas JB, Harder B (2003) Ophthalmodynamometric estimation of cerebrospinal fluid pressure in pseudotumour cerebri. Br J Ophthalmol 87(3):361–362
47. Poca MA, Sahuquillo J, Topczewski T, Lastra R, Font ML, Corral E (2006) Posture-induced changes in intracranial pressure: a comparative study in patients with and without a cerebrospinal fluid block at the craniovertebral junction. Neurosurgery 58(5):899–906 (discussion 899–906). doi:10.1227/01.NEU.0000209915.16235.6D
48. Maira G, Anile C, Cioni B, Menini E, Mancini A, De Marinis L, Barbarino A (1984) Relationships between intracranial pressure and diurnal prolactin secretion in primary empty sella. Neuroendocrinology 38(2):102–107
49. Cruickshank A, Auld P, Beetham R, Burrows G, Egner W, Holbrook I, Keir G, Lewis E, Patel D, Watson I, White P (2008) Revised national guidelines for analysis of cerebrospinal fluid for bilirubin in suspected subarachnoid haemorrhage. Ann Clin Biochem 45(Pt 3):238–244. doi:10.1258/acb.2008.007257
50. Beetham R (2009) CSF spectrophotometry for bilirubin–why and how? Scand J Clin Lab Invest 69(1):1–7. doi:10.1080/00365510802651866
51. Chow SL, Rooney ZJ, Cleary MA, Clayton PT, Leonard JV (2005) The significance of elevated CSF lactate. Arch Dis Child 90(11):1188–1189. doi:10.1136/adc.2005.075317
52. Aburahma S, Khassawneh M, Griebel M, Sharp G, Gibson J (2011) Pitfalls in measuring cerebrospinal fluid glycine levels in infants with encephalopathy. J Child Neurol 26(6):703–706. doi:10.1177/0883073810389041
53. Schmiedel J, Jackson S, Schafer J, Reichmann H (2003) Mitochondrial cytopathies. J Neurol 250(3):267–277. doi:10.1007/s00415-003-0978-3
54. Kurian MA, Gissen P, Smith M, Heales S Jr, Clayton PT (2011) The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. Lancet Neurol 10(8):721–733. doi:10.1016/S1474-4422(11)70141-7
55. Link H, Huang YM (2006) Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J Neuroimmunol 180(1–2):17–28. doi:10.1016/j.jneuroim.2006.07.006
56. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69(2):292–302. doi:10.1002/ana.22366
57. Psimaras D, Carpentier AF, Rossi C (2010) Cerebrospinal fluid study in paraneoplastic syndromes. J Neurol Neurosurg Psychiatry 81(1):42–45. doi:10.1136/jnnp.2008.159483
58. Jedryka-Goral A, Zabek J, Wojciechowski B, Zaborski J, Chwalinska-Sadowska H, Czlonkowska A (2000) Evaluation of cerebrospinal fluid for the presense of anticardiolipin antibodies (aCL) in NP-SLE patients. Clin Rheumatol 19(4):306–310
59. Joseph FG, Scolding NJ (2009) Neurosarcoidosis: a study of 30 new cases. J Neurol Neurosurg Psychiatry 80(3):297–304. doi:10.1136/jnnp.2008.151977
60. Scolding NJ, Jayne DR, Zajicek JP, Meyer PA, Wraight EP, Lockwood CM (1997) Cerebral vasculitis–recognition, diagnosis and management. Qjm 90(1):61–73

61. Al-Araji A, Kidd DP (2009) Neuro-Behcet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol 8(2):192–204. doi:10.1016/S1474-4422(09)70015-8
62. Glantz MJ, Cole BF, Glantz LK, Cobb J, Mills P, Lekos A, Walters BC, Recht LD (1998) Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. Cancer 82(4):733–739
63. Joseph FG, Scolding NJ (2007) Sarcoidosis of the nervous system. Pract Neurol 7(4):234–244. doi:10.1136/jnnp.2007.124263
64. Porter MJ, Brookes GB, Zeman AZ, Keir G (1992) Use of protein electrophoresis in the diagnosis of cerebrospinal fluid rhinorrhoea. J Laryngol Otol 106(6):504–506
65. Sinclair AJ, Viant MR, Ball AK, Burdon MA, Walker EA, Stewart PM, Rauz S, Young SP (2009) NMR-based metabolomic analysis of cerebrospinal fluid and serum in neurological diseases—a diagnostic tool? NMR Biomed 23(2):123–132. doi:10.1002/nbm.1428
66. Metzger G, Singbartl G (1991) Spinal epidural hematoma following epidural anesthesia versus spontaneous spinal subdural hematoma. Two case reports. Acta Anaesthesiol Scand 35(2):105–107
67. (2004) The International Classification of Headache Disorders: 2nd edn. Cephalalgia 24 (Suppl 1):9–160
68. Winsvold BS, Hagen K, Aamodt AH, Stovner LJ, Holmen J, Zwart JA (2011) Headache, migraine and cardiovascular risk factors: the HUNT study. Eur J Neurol 18(3):504–511. doi:10.1111/j.1468-1331.2010.03199.x
69. Handler CE, Smith FR, Perkin GD, Rose FC (1982) Posture and lumbar puncture headache: a controlled trial in 50 patients. J R Soc Med 75(6):404–407
70. Dieterich M, Brandt T (1985) Is obligatory bed rest after lumbar puncture obsolete? Eur Arch Psychiatry Neurol Sci 235(2):71–75
71. Vilming ST, Schrader H, Monstad I (1988) Post-lumbar-puncture headache: the significance of body posture. A controlled study of 300 patients. Cephalalgia Int J Headache 8(2):75–78
72. Machurot PY, Vergnion M, Fraipont V, Bonhomme V, Damas F (2010) Intracranial subdural hematoma following spinal anesthesia: case report and review of the literature. Acta Anaesthesiol Belg 61(2):63–66
73. Amorim JA, Remigio DS, Damazio Filho O, de Barros MA, Carvalho VN, Valenca MM (2010) Intracranial subdural hematoma post-spinal anesthesia: report of two cases and review of 33 cases in the literature. Rev Bras Anestesiol 60(6):620–629
74. Arendt K, Demaerschalk BM, Wingerchuk DM, Camann W (2009) Atraumatic lumbar puncture needles: after all these years, are we still missing the point? Neurologist 15(1):17–20. doi:10.1097/NRL.0b013e318184f476
75. Strupp M, Brandt T, Muller A (1998) Incidence of post-lumbar puncture syndrome reduced by reinserting the stylet: a randomized prospective study of 600 patients. J Neurol 245(9):589–592
76. Dieterich M, Brandt T (1988) Incidence of post-lumbar puncture headache is independent of daily fluid intake. Eur Arch Psychiatry Neurol Sci 237(4):194–196
77. Camann WR, Murray RS, Mushlin PS, Lambert DH (1990) Effects of oral caffeine on postdural puncture headache. A double-blind, placebo-controlled trial. Anesth Analg 70(2):181–184
78. Vilming ST, Kloster R, Sandvik L (2005) When should an epidural blood patch be performed in postlumbar puncture headache? A theoretical approach based on a cohort of 79 patients. Cephalalgia Int J Headache 25(7):523–527. doi:10.1111/j.1468-2982.2005.00911.x
79. Martin R, Jourdain S, Clairoux M, Tetrault JP (1994) Duration of decubitus position after epidural blood patch. Can J Anaesth 41(1):23–25. doi:10.1007/BF03009656
80. Duffy PJ, Crosby ET (1999) The epidural blood patch. Resolving the controversies. Can J Anaesth 46(9):878–886. doi:10.1007/BF03012979
81. Abouleish E, Vega S, Blendinger I, Tio TO (1975) Long-term follow-up of epidural blood patch. Anesth Analg 54(4):459–463
82. Woodworth GF, McGirt MJ, Williams MA, Rigamonti D (2009) Cerebrospinal fluid drainage and dynamics in the diagnosis of normal pressure hydrocephalus. Neurosurgery 64(5):919–925 (discussion 925–916). doi:10.1227/01.NEU.0000341902.44760.10
83. Gallia GL, Rigamonti D, Williams MA (2006) The diagnosis and treatment of idiopathic normal pressure hydrocephalus. Nat Clin Pract Neurol 2(7):375–381. doi:10.1038/ncpneuro0237
84. Solana E, Poca MA, Sahuquillo J, Benejam B, Junque C, Dronavalli M (2010) Cognitive and motor improvement after retesting in normal-pressure hydrocephalus: a real change or merely a learning effect? J Neurosurg 112(2):399–409. doi:10.3171/2009.4.JNS081664
85. Baer ET (2006) Post-dural puncture bacterial meningitis. Anesthesiology 105(2):381–393
86. van de Beek D, Drake JM, Tunkel AR (2010) Nosocomial bacterial meningitis. N Engl J Med 362(2):146–154. doi:10.1056/NEJMra0804573
87. Dakka Y, Warra N, Albadareen RJ, Jankowski M, Silver B (2011) Headache rate and cost of care following lumbar puncture at a single tertiary care hospital. Neurology 77(1):71–74. doi:10.1212/WNL.0b013e318220abc0
88. Zetterberg H, Tullhog K, Hansson O, Minthon L, Londos E, Blennow K (2010) Low incidence of post-lumbar puncture headache in 1,089 consecutive memory clinic patients. Eur Neurol 63(6):326–330. doi:10.1159/000311703
89. Vallejo MC, Mandell GL, Sabo DP, Ramanathan S (2000) Postdural puncture headache: a randomized comparison of five spinal needles in obstetric patients. Anesth Analg 91(4):916–920
90. Strupp M, Schueler O, Straube A, Von Stuckrad-Barre S, Brandt T (2001) "Atraumatic" Sprotte needle reduces the incidence of post-lumbar puncture headaches. Neurology 57(12):2310–2312
91. Hammond ER, Wang Z, Bhulani N, McArthur JC, Levy M (2011) Needle type and the risk of post-lumbar puncture headache in the outpatient neurology clinic. J Neurol Sci 306(1–2):24–28. doi:10.1016/j.jns.2011.04.004
92. Kleyweg RP, Hertzberger LI, Carbaat PA (1998) Significant reduction in post-lumbar puncture headache using an atraumatic needle. A double-blind, controlled clinical trial. Cephalalgia Int J Headache 18(9):635–637 (discussion 591)
93. Lavi R, Yarnitsky D, Rowe JM, Weissman A, Segal D, Avivi I (2006) Standard vs atraumatic Whitacre needle for diagnostic lumbar puncture: a randomized trial. Neurology 67(8):1492–1494. doi:10.1212/01.wnl.0000240054.40274.8a
94. Ellenby MS, Tegtmeyer K, Lai S, Braner DA (2006) Videos in clinical medicine. Lumbar puncture. N Engl J Med 355(13):e12. doi:10.1056/NEJMvcm054952
95. Clarke C, Howard R, Rossor M, Shorvon S (2009) Neurology: a queen square textbook, 1st edn. Wiley-Blackwell, UK