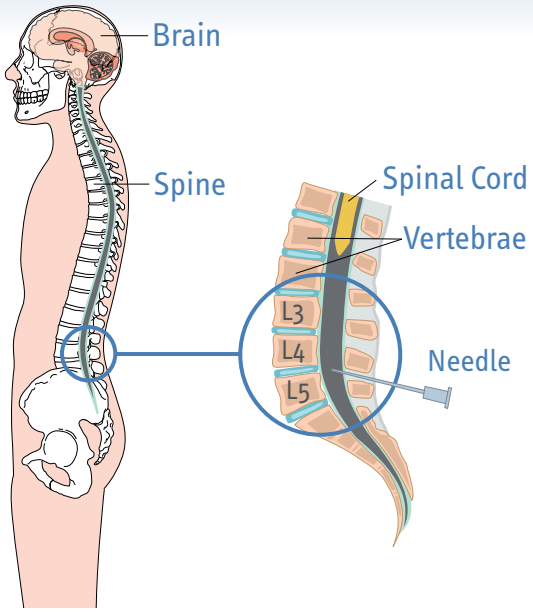
Illustration of CSF collection



Shipment of cerebrospinal fluid samples

- **If the laboratory is located within your center:**
  Bring the CSF sample immediately to the laboratory (in the PP tube, at room temperature).
- **If the laboratory is located outside your center with sample pretreatment on site:**
  Bring the CSF sample immediately to the laboratory (in the PP tube, at room temperature). The local laboratory deals with centrifugation, decantation and shipping within 24 hours at room temperature, or freezing of the sample in case of delayed shipment.
- **If the laboratory is located outside your center without sample pretreatment on site:**
  Send the CSF sample to the laboratory in charge of the assay within 4h after the LP (in the PP tube, at room temperature). The sampling and shipment hours should be reported for traceability.

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Practical guide for lumbar puncture

Biomarkers for Alzheimer's disease in cerebrospinal fluid

Claire Paquet

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Before suggesting a lumbar puncture...

- **Evaluate the rachis accessibility:**
  In case of difficult access (when the intervertebral space is not palpable): consider for lumbar puncture (LP) under scopy.

- **Look for contraindications:**
  - Clotting problems (according to literature: thrombopenia <60000[1], thrombopenia 60000 with an increased bleeding time, PT, INR (>1,5) and/or PTT abnormalities)[2] or anticoagulant treatment.
  - Rachidian plaque, behavioural disorder.
  - Significantly increased intracranial pressure or any intracranial mass effect on imaging.
  - Skin infections or developmental anomalies (myelomeningocele) at the entrance site of the needle.

To do a lumbar puncture

- **Check haemostasis and brain imaging.**
- **Treatment with low molecular weight heparin should be stopped before LP[2-3]:**
  - 12h in case of prophylactic dose
  - 24h in case of hypocoagulant dose
- **Do the LP collection in the morning[4].**
- **Use local anesthesia** (e.g. 1% lidocaine) or EMLA™ patch (at least 1h before LP). If necessary, give analgesic/sedative gas (e.g. Kalinox®) and/or low dose of anxiolytic drugs.
- **All the necessary material must be ready on a trolley:** trash can, sterile gloves and mask, antiseptic solution, physiological salt solution, sterile compresses, dressing, dedicated needle for LP, polypropylene (PP) tubes indicated by your laboratory and tubes for biochemistry, bacteriology, cytology.
- **Position of the patient:** sitting or lying down in lateral recumbent position, with rachis parallel to the bed. In this position, look for the L4L5 lumbar space (centre of line joining the two posterior iliac crests) or the L3L4 lumbar space above.
- **Disinfect the skin around the entrance site of the needle according to your standard procedure.**
- **Lumbar puncture procedure:** Do not touch the metal part of the needle. Orient the bevel parallel to the longitudinal dural fibers. Insert the needle forwards, with a slight angle upwards. Advance slowly but smoothly. A resistance change is felt when inserting the needle through the yellow ligament, with a characteristic “pop” when the needle penetrates the dura. The stylet should be withdrawn and observed for fluid return.
- **If heparinotherapy is necessary, post-LP introduction should be delayed at least 1h to minimize the risk of hematoma[1;3;5].**
- **For cerebrospinal fluid (CSF) biomarkers (Alzheimer-specific proteins):**
  - do not use the 20 first drops
  - collect CSF (≥4 ml) directly in the PP tube
- **At the end of CSF sampling, replace the stylet and remove the needle.** Clean the skin and apply a sterile dressing.
- **Place the patient in a supine position.** The patient should refrain from any physical activity for 24 hours or long travels.
- **Prescribe simple analgesics, if needed.**

Side effects of a lumbar puncture

- **Post-LP syndrome:**
  the most frequent side effect, characterized by the appearance of an orthostatic headache is relieved by decubitus[6]. The intensity varies from mild to moderate. The headache can be frontal or occipital with irradiations to the neck and shoulders[6-8]. Post-LP syndrome can be accompanied by lumbar pain, dizziness, nausea, light and sound phobia, and exceptionally, paralysis of the brain nerves[9-13]. In 90% of cases, side effects will appear within 72h after the LP[14-15].
  Risk factors for post-LP syndrome include:
  - the patient’s age: 10 to 15% in young patients, <5% in patients ≥65 years old, 2% in case of dementia[16]
  - low BMI[17]

- **Epidural or spinal subdural hematoma:**
  of the 49 cases reported, 46% had trombocytopenia, 36% had heparin treatment before or after the LP, 75% occurred after difficult or traumatic LP. To be evoked if there is a lumbar pain with paresthesias and/or paraparesis (therapeutic emergency)[18-40].

- **Intracranial subdural hematoma:**
  8 cases described. To investigate if the post-LP syndrome lasts for more than 8 days or in case of loss of postural character of headache or appearance of localization signs[33;41-50].

- **Intracranial hypotension post-LP[51-52].**

- **Dural abscess, pneumocephalus[53-54], meningitis[36-37].**

To prevent side effects

- Use an atraumatic needle or a narrow beveled needle (black/22gauge)[8;55-56] introduction of the needle with upward inclination, minimizing the opening in the dura by squeezing the needle between dural fibers and repositioning of the stylet at the end of the LP[57-60].
- Some studies have shown the benefit of a pretreatment with IV caffeine[8;61-62].

Note

- Collected volume of CSF (if <30ml), number of attempts, patient position, duration of rest following LP, patient hydration, did not show any influence on the occurrence of a post-LP syndrome[59-60;63-64].
- There is neither consensus nor a risk-benefit study on performing the LP under anti-aggregant therapy.
- Migraine is not a related risk of CSF collection[17].
- In case of a severe post-LP syndrome, treatment with a blood-patch is effective.

Link with Alzheimer’s disease

- The concentration of specific biomarkers in CSF (amyloid peptide, total and phosphorylated tau protein) reflects a biochemical change due to brain damage characteristic for Alzheimer’s disease.
- Using these CSF biomarkers, Alzheimer’s disease can be diagnosed accurately and early[65-67].
- There may be a time lag between obvious pathophysiology and its symptomatic expression, making alterations in biomarker concentrations one of the first signs of Alzheimer’s disease.

Biomarkers for Alzheimer’s disease in cerebrospinal fluid