Title page

Manuscript title: CSF Lactate

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How to use it: CSF Lactate

Abstract

Lactate is produced from anaerobic glycolysis, which occurs in most tissues in the human body. Blood lactate is tested in most physiologically unwell patients in the Emergency Department and helps to guide treatment and prognosis. Cerebrospinal fluid (CSF) lactate, however, is infrequently measured. A raised CSF lactate occurs in various central nervous system conditions, including acute neurological infection, stroke, seizures and mitochondrial pathologies. This article discusses the utility and limitations of CSF lactate, highlighting specific clinical situations where it can help the diagnosis of central nervous system infections and unexplained encephalopathy.

Introduction

Lactate is produced by most tissues in the body. Under anaerobic conditions, it is the end product of glycolysis, with pyruvate being converted to lactic acid by lactate dehydrogenase. In aqueous solutions, lactic acid dissociates almost completely into lactate and H+. Thus, the terms 'lactate' and 'lactic acid' are used somewhat interchangeably. In plasma, lactate is buffered by HCO_3–. Many pathologies can result in its accumulation.

Lactate exists in two optical isomeric forms:

- **L-lactate** is the isomer measured on the commonly used assays and this is the only form produced by human metabolism.
- **D-lactate** is produced by bacterial metabolism and can accumulate in patients with short-gut syndrome or a history of gastric bypass. The accumulation of D-lactate is a rare cause of encephalopathy with high anion gap metabolic acidosis.

Blood lactate is tested in most physiologically unwell patients in the Emergency Department, where it helps to guide treatment and prognosis. In contrast, cerebrospinal fluid (CSF) lactate is rarely tested.

CSF Lactate

CSF lactate concentration depends largely on its production from CNS glycolysis. Its value is independent of blood lactate, probably because lactate in its ionised state crosses the blood–CSF barrier very slowly. CSF lactate measurement requires only a standard laboratory analyser and, depending on the laboratory, has a rapid turnaround (within 2 hours).[1] It is inexpensive (average £5 in the UK) and has high test–retest reliability. It also available in the resource-poor world, where neurological imaging may be difficult to obtain. The tested sample should ideally be the least blood-stained fraction of CSF (as red blood cells contain large amounts of lactate) taken in a fluoride tube (grey top) with a minimum sample volume of 0.5 ml. It should reach the laboratory promptly following sampling (ideally within 60 minutes) and should be frozen if analysis is to be delayed for >24 hours, as otherwise the result can be spuriously elevated.

The CSF lactate reference range for adults and older children is typically set as 1.2–2.1mmol/L, although the published literature cites ranges of 0.6–3.1mmol/L. Neonates have a higher upper limit

of normal at 3 mmol/L. The normal range for blood lactate is 0.5–1.0 mmol/L; values below 2mmol/L are considered normal in people with critical illness.

A range of CNS pathologies can increase the CSF lactate concentration (see box 1), including intracranial infection, seizures (in particular status epilepticus and focal seizures with loss of awareness), stroke and mitochondrial disorders.[2]

Box 1: Causes of an elevated CSF Lactate

- Intracranial infection (bacterial, mycobacterial and fungal)
- Seizures (in particular status epilepticus and focal seizures with loss of consciousness)
- Stroke
- Malignancy
- Mitochondrial disorders
- Inherited metabolic disorders
- Subarachnoid haemorrhage
- Traumatic brain injury
- Anoxic brain injury
- Hypoglycaemic coma

Intracranial infection

Distinguishing community-acquired acute bacterial meningitis from viral meningitis

A 38-year-old man was admitted via the Emergency Department with headache, neck stiffness, photophobia and painful eye movements. He had been previously well. An urgent CT scan of the head was normal. CSF showed a white cell count of 87 cells/mm^3 with neutrophil predominance (80%), CSF protein of 0.7g/L and glucose of 3.2mmol/L (plasma 5.0 mmol/L). CSF lactate was 1.7 mmol/L. Enterovirus PCR subsequently returned positive in CSF confirming the diagnosis of enterovirus meningitis.

Acute bacterial meningitis is a life-threatening medical emergency where rapid diagnosis and promptly starting antibiotics is lifesaving. In contrast, acute viral meningitis is usually self-limiting. In practice, many patients with viral meningitis are started on antibiotics when these are not indicated, giving associated risks of antimicrobial resistance, nosocomial infections, elevated hospital costs and prolonged length of stay.

CSF lactate is elevated in both bacterial (including tuberculous) and fungal meningitides. There are many reasons for the elevated CSF lactate, including direct bacterial production, but also cerebral oedema, vascular inflammation and cerebral ischaemia which each result in a shift towards anaerobic metabolism and so an increased lactate production.

Several prospective and retrospective studies, and a well-designed meta-analysis, have shown that a CSF lactate of ≥3.5 mmol/L has a high sensitivity (96–99%) and specificity (88–94%) for distinguishing acute bacterial meningitis from acute viral meningitis, and is better than other measurements that are classically used to guide decisions in people with suspected acute meningitis.[3,4] A rapidly falling CSF lactate (if there have been multiple CSF examinations) also suggests a good prognosis in people with acute bacterial meningitis.[4]

Conventional CSF markers, such as white cell count and differential, and CSF: blood glucose ratio each have poor specificity. For instance, patients with enterovirus meningitis (as in the case above) may have a CSF profile that would otherwise indicate bacterial meningitis. In such cases, CSF lactate, with its high negative predictive value, can be very useful in assisting the diagnosis and so help decision making to stop or withhold antibiotics.

Clinicians should diagnose and manage suspected acute bacterial meningitis according to agreed guidelines, such as the British Infection Association consensus guidelines. These advise testing CSF lactate only on samples obtained before giving antibiotics, as its sensitivity drops significantly (to less than 50%) after they are started.[5]

Other CSF biochemistry measurements, especially protein and glucose, should be used together with CSF lactate to inform the likely diagnosis in the acute setting. Unfortunately, a paired blood glucose is often not sent contemporaneously and a CSF glucose without a paired blood sample has a poor sensitivity for identifying patients with acute bacterial meningitis.[5,7] As CSF lactate is independent of blood lactate, it does not require paired blood sampling.[2]

It is important to remember that other pathologies (box 1) can elevate the CSF lactate and it must be interpreted in clinical context.

Bacterial meningitis following neurosurgical intervention

A 45-year-old man underwent a craniotomy and external ventricular drain insertion following aneurysmal subarachnoid haemorrhage. Three days post-operatively, he became febrile and his Glasgow Coma Scale score dropped. His CSF white cell count was 27 cells/mm^3, CSF protein was 0.7g/L, and CSF glucose was 2.2mmol/L (paired blood glucose 5.8mmol/L). His CSF lactate was raised at 8.7mmol/L. He was started on antibiotics for a presumed post-operative nosocomial bacterial meningitis, and his CSF subsequently grew Staphylococcus aureus.

Bacterial meningitis following neurosurgical intervention is not uncommon, developing in 0.3–8.6% of patients following craniotomy.[8] The diagnosis is often a clinical challenge as it is difficult to distinguish from post-neurosurgical “chemical/aseptic meningitis”. CSF inflammatory and biochemical profiles often mimic those seen post-neurosurgical intervention; in such situations, CSF lactate has a high negative predictive value and can allow clinicians to make a more confident diagnosis and prevent them prematurely stopping antibiotics. A CSF lactate of ≥4mmol/L in patients with suspected post-neurosurgical bacterial meningitis has a better predictive value than either CSF pleocytosis or hypoglycorrhacia.[9, 10]

CSF lactate may also help in diagnosis of internalised CSF shunt infections. These are common, occurring with 5–15% of inserted devices and are particularly common in the first four weeks following placement.[11] CSF lactate is a useful adjunct to other clinical investigations for making the

diagnosis of internalised shunt infections, but the data on this is not consistent. In patients with a low likelihood of infection, a high CSF lactate should prompt reconsideration; however, if infection is very likely then a low value should not dismiss the diagnosis (particularly if the patient is already on anti-microbial treatment).[11]

Mitochondrial encephalopathy

A 50-year-old woman presented to the emergency department with acute confusion and agitation. She had a background of longstanding sensorineural hearing loss and diabetes mellitus requiring insulin. MR scan of brain showed cortical and subcortical oedema involving the right and left temporal and parietal lobes. The initial differential diagnosis was broad and included an infectious and immune-mediated encephalitides and metabolic causes. CSF showed a normal white cell count, protein and glucose. CSF lactate was elevated at 5.1 mmol/L. Blood lactate was within normal limits. The elevated CSF lactate pointed towards a possible mitochondrial disorder. Further investigation confirmed a diagnosis of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).

A common clinical scenario for the general neurologist is the acutely confused patient - CSF lactate can be a useful diagnostic adjunct in patients with unexplained encephalopathy. These patients are often empirically treated for herpes simplex virus (HSV) encephalitis and the question of autoimmune limbic encephalitis frequently remains in the differential diagnosis. The CSF lactate is typically minimally elevated (<3.5mmol/l) in patients with HSV encephalitis and therefore, a markedly elevated CSF lactate would indicate a bacterial CNS infection or rarer pathologies, such as mitochondrial encephalopathy (see case above). Similarly, patients with autoimmune limbic encephalitis typically have a normal CSF lactate, thus a markedly elevated CSF lactate would be a pointer towards other aetiologies. However, seizures (both focal and generalised) may occur in both these pathologies and can result in elevation of the CSF lactate, potentially misleading the investigating team.

In primary mitochondrial diseases, elevated lactate results from increased flux through glycolysis, which overwhelms the mitochondrial utilisation of pyruvate. In patients with neurological symptoms, elevated CSF lactate can therefore be a useful signature of an underlying mitochondrial pathology.[12]

Although a high blood or CSF lactate may be a consequence of underlying mitochondrial dysfunction, it is a non-specific finding. Furthermore, primary mitochondrial diseases can have normal, or only mildly elevated, blood and CSF lactates, including *POLG*-related mitochondrial disorders, Leber hereditary optic neuropathy, Leigh disease, and Kearns–Sayre syndrome.[13]

Conclusion

We have highlighted several situations where CSF lactate can help the clinical neurologist. It is an inexpensive test with a swift turn-around time that does not require a paired blood sample sent. It can be a useful adjunct to the diagnosis of community acquired bacterial meningitis and may help confirm suspicion of acute viral meningitis allowing early halting of antimicrobials. It is helpful in the post-operative situation, distinguishing "chemical/aseptic meningitis" from nosocomial infection and

has utility at identifying shunt infections. Rarely, in cases of unexplained encephalopathy, it may be elevated in mitochondrial disease.

It is rarely used, yet can inform both diagnosis and management.

Key points

- CSF lactate is an inexpensive test which can be very useful for diagnosis in the appropriate clinical context
- In patients with suspected community-acquired acute meningitis, a CSF lactate of ≥3.5 mmol/L has a high sensitivity and specificity for distinguishing bacterial from viral causes
- CSF lactate can be useful in distinguishing post-neurosurgical bacterial meningitis from "chemical/aseptic meningitis" post-surgical intervention
- CSF lactate can be a useful diagnostic pointer for mitochondrial disorders and inherited metabolic disorders

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Figure legends

Figure 1: The chemical structure of the lactate ion

Figure 2: Overview of the lactic acid cycle

The breakdown of glycogen in skeletal muscle (by glycogenolysis) results in the release of glucose in the form glucose-1-phosphate, which is subsequently converted to glucose-6-phosphate. Glucose 6-phosphate then enters glycolysis. In the presence of oxygen, glucose 6-phosphate is converted to pyruvate, which enters the Krebs' cycle. However, in anaerobic conditions, pyruvate is converted to lactate (by lactate dehydrogenase). Lactate is taken up by the liver where gluconeogenesis occurs and is converted first to pyruvate and then to glucose.