Cerebrospinal Fluid in Long-Lasting Delirium Compared With Alzheimer’s Dementia

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Background. Delirium is a common syndrome affecting older people in hospital, whose pathophysiology is poorly understood, but sequelae of increased cognitive and functional impairment suggest neuronal loss.

Methods. Cohort study comparing cerebrospinal fluid, blood, and clinical markers of delirium and neuronal cell death in 20 older hospitalized patients with delirium and 20 outpatients with Alzheimer’s dementia.

Results. Compared with participants with dementia, patients with delirium demonstrated higher CSF lactate (1.87 vs 1.48 mmol/L, p < .001) and protein levels (0.62 vs 0.44 g/L, p = .036) and lower levels of neuron-specific enolase (4.84 vs 8.98 ng/mL, p < .001) but no difference in S100B. The changes correlated with clinical indices and outcomes.

Conclusion. Older patients with delirium experience significant metabolic disturbance in the brain, which requires further investigation.

Key Words: Delirium—Dementia—Lactic acid—Neuron-specific enolase—S100 proteins.

Received October 2, 2009; Accepted April 23, 2010

Decision Editor: Luigi Ferrucci, MD, PhD

Delirium is a common syndrome of acute confusion, fluctuating level of consciousness, and decreased attention, with 10%–24% of hospitalized older patients admitted with incidental delirium and a further 56% developing the condition during hospitalization (1). Delirium leads to increased mortality, impairment of activities of daily living and cognitive decline (2), increased length of hospital stay and nursing home placements (3), as well as the development of dementia (4).

The pathophysiology of delirium remains poorly understood. Altered neurotransmitter levels are commonly implicated (5), but recent work has found altered oxidative markers (6) and abnormal serum inflammatory markers, including raised eotaxin and C-C motif ligand (CCL)-2 (7), raised interleukin-6 and interleukin-8 (8), lower insulin-like growth factor-1 and interleukin-1RA (9), and raised S100B (10), in groups with delirium, but the articles report no correlation with clinical outcomes apart from cognitive changes involved in diagnosis of delirium to ensure that changes are clinically significant, and so it is unclear whether these are etiological changes or epiphenomena.

The outcomes of delirium, especially increased activities of daily living and cognitive impairment, suggest neuronal loss and underscore the link with dementia for which these are core features. Delirium may therefore offer insights into the progression of dementia and may, perhaps, be one of the acute drivers of dementia where neuronal cell death is undeniable but poorly understood (11). Clinically, delirium is often confused with dementia (1), so we have selected a group of patients with Alzheimer’s dementia as controls. Therefore, we have investigated a hypothesis that delirium is caused by acute episodes of neuronal cell death using cerebrospinal fluid (CSF) markers of cell death: lactate, neuron-specific enolase (NSE), and S100B, and examined whether there is any relationship between these measures and outcomes of delirium. Additionally, these markers may offer insights into the etiology of increased reactive oxygen species (12) and glucose hypometabolism, which are seen in dementia and mild cognitive impairment (13).

Methods

Patients admitted to the Geriatric Medicine Unit at Prince of Wales Hospital were screened for delirium in the Emergency Department and on the Geriatric Medicine ward. Patients suffering from delirium, which did not resolve after >5 days of treatment, were considered for further investigation, including lumbar puncture, and this was discussed with their “person responsible” or substitute decision maker and the patient where possible. Patients were suffering from a variety of active diagnoses, including cardiac diseases (11 patients), infection (10), electrolyte abnormalities (10),
acutely distributed continuous variables were compared using

By using a technique that has to approve interventional studies involving partic-


cipants who are unable to give consent, but not observational

	hestudies, and no objections were raised. SPSS (version 17;


SPSS Inc, Chicago, IL) was used for statistical analyses. Nor-


mally distributed continuous variables were compared using


t tests. Correlation coefficients were used to compare con-


tinuous variables. All statistical tests were two-tailed with a


p value < .05 considered significant.


RESULTS

Baseline characteristics showed that the two groups were


well matched for age, IADL, Charlson Index, Informant Ques-


tionnaire on Cognitive Decline in the Elderly, and Geriatric Depress-


ion Scale. The delirium group had lower Barthel and Mini-Mental State


Examination scores but higher Confusion Assessment Method, Delirium Index, and


Acute Physiology and Chronic Health Evaluation scores (Table 1).


CSF lactate was raised in the delirium group compared with those with Alzheimer’s dementia, whereas NSE levels were lower, though there was no difference in CSF glucose. We also found a higher level of CSF protein (Table 2). There


<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>Dementia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>81.6 (7.7)</td>
<td>81.1 (6.1)</td>
<td>.839</td>
</tr>
<tr>
<td>Barthel Index/20</td>
<td>18.2 (2.8)</td>
<td>19.8 (0.6)</td>
<td>.037</td>
</tr>
<tr>
<td>Change in Barthel during admission</td>
<td>6.6 (7.2)</td>
<td>3.6 (3.8)</td>
<td>.168</td>
</tr>
<tr>
<td>IADL (/12)</td>
<td>6.7 (3.8)</td>
<td>8.6 (3.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Change in IADL during admission</td>
<td>3.6 (3.8)</td>
<td>.295</td>
<td></td>
</tr>
<tr>
<td>Charlson Index</td>
<td>6.5 (1.9)</td>
<td>6.4 (2.2)</td>
<td>.894</td>
</tr>
<tr>
<td>APACHE III</td>
<td>46.1 (18.3)</td>
<td>33.0 (9.6)</td>
<td>.039</td>
</tr>
<tr>
<td>IQCODE (/5)</td>
<td>3.7 (0.5)</td>
<td>3.7 (0.5)</td>
<td>.862</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>16.9 (3.7)</td>
<td>22.8 (4.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Confusion Assessment Method</td>
<td>4.6 (2.2)</td>
<td>0.0 (0.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delirium Index</td>
<td>13.8 (4.3)</td>
<td>2.7 (1.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>6.5 (1.8)</td>
<td>6.8 (3.0)</td>
<td>.796</td>
</tr>
</tbody>
</table>

Note: APACHE = Acute Physiology and Chronic Health Evaluation; IADL = instrumental activities of daily living; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly.

<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>Dementia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF lactate (mmol/L)</td>
<td>1.87 (0.31)</td>
<td>1.48 (0.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CSF protein (g/L)</td>
<td>0.62 (0.33)</td>
<td>0.44 (0.15)</td>
<td>.036</td>
</tr>
<tr>
<td>CSF glucose (mmol/L)</td>
<td>3.90 (0.95)</td>
<td>3.65 (1.48)</td>
<td>.54</td>
</tr>
<tr>
<td>CSF S100B (pg/mL)</td>
<td>604.8 (163.0)</td>
<td>697.4 (306.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CSF S100B (pg/mL) median (interquartile range)</td>
<td>60.1 (462.7–700.6)</td>
<td>612.5 (504.7–774.5)</td>
<td></td>
</tr>
<tr>
<td>CSF neuron-specific enolase (ng/mL)</td>
<td>4.84 (2.02)</td>
<td>8.98 (2.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.78 (1.62)</td>
<td>1.26 (0.39)</td>
<td>.295</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>59.44 (7.50)</td>
<td>66.94 (3.86)</td>
<td>.001</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.12 (1.50)</td>
<td>5.87 (2.35)</td>
<td>.801</td>
</tr>
<tr>
<td>S100B (pg/mL) median (interquartile range)</td>
<td>0.053 (0.0–0.025)</td>
<td>0.024 (0.002–0.173)</td>
<td></td>
</tr>
</tbody>
</table>

Note: CSF = cerebrospinal fluid.
was a strong negative correlation between CSF lactate and NSE (Pearson correlation coefficient [PCC] −0.717, p < .001). CSF lactate was correlated with serum lactate (PCC 0.481, p = .020), but there were two participants whose serum lactate was around 3 SDs above the mean who were considered outliers, and after excluding them, the correlation was no longer significant (PCC 0.155, p = .52; Figure 1). There was no difference in CSF S100B levels (Table 2).

Positive correlations were found between CSF lactate and the Acute Physiology and Chronic Health Evaluation score, Confusion Assessment Method, and Delirium Index. NSE did not correlate with the Acute Physiology and Chronic Health Evaluation score but did with the Confusion Assessment Method and Delirium Index, though not as strongly as lactate (Table 3).

In the delirium group, CSF lactate correlated with a greater decrease in IADL scores from admission to discharge and a trend toward greater decrease in the Barthel Index, which indicate greater functional decline (Table 3; Figures 2 and 3). CSF protein did not correlate with changes in IADL or Barthel Index, whereas there was a significant negative correlation between CSF glucose and change in Barthel Index, although not IADL (Figures 4–7).

Over all participants, there was no significant correlation between CSF lactate and CSF glucose (PCC 0.265, p = .082), though CSF glucose was highly correlated with blood glucose (PCC 0.799, p < .001). However, within the delirium group, comparing the subgroup who died in hospital with those discharged home revealed higher CSF lactate levels (2.15 ± 0.17 vs 1.77 ± 0.26 mmol/L, p = .029) as well as lower CSF glucose (3.30 ± 0.58 vs 4.56 ± 0.93 mmol/L, p = .028) and higher CSF protein (0.81 ± 0.32 vs 0.46 ± 0.17, p = .020). For those who died, the average time from their lumbar puncture to death was 14 days (range 8–22 days). A group who were discharged to nursing homes were intermediate, but not significantly different, from the two other groups.

**DISCUSSION**

We found that older medical patients in hospital with delirium had elevated CSF lactate and protein and decreased CSF NSE compared with a control group of outpatients with dementia and that these changes correlated with their clinical condition and outcomes. There was no change found in CSF S100B levels.

We have studied a nondiagnosis-specific group of older patients with delirium. These patients generally had multiple problems including infection, biochemical derangements, and polypharmacy, including cholinergic drugs. Their clinical episode of delirium included hyperactive and hypoactive periods, and some of them were treated with antipsychotic and other sedative medication in an attempt to treat their delirium and minimize self-harm. Many studies have looked at single diagnostic groups, for example, cardiac surgery patients (7); however, older medical patients usually have multifactorial delirium and a nondiagnosis-specific group better reflects the real world of delirium.

**Table 3. Correlation Coefficients Between Clinical Indices and Cerebrospinal Fluid Markers**

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
<th>Delirium Group Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confusion Assessment</td>
<td>Delirium Index</td>
</tr>
<tr>
<td>Lactate</td>
<td>.001</td>
<td>.703</td>
</tr>
<tr>
<td>Neuron-specific enolase</td>
<td>.415</td>
<td>.467</td>
</tr>
<tr>
<td>S100B</td>
<td>.003</td>
<td>.378</td>
</tr>
<tr>
<td>Protein</td>
<td>.992</td>
<td>.135</td>
</tr>
<tr>
<td>Glucose</td>
<td>.048</td>
<td>.458</td>
</tr>
</tbody>
</table>

Note: APACHE = Acute Physiology and Chronic Health Evaluation; CSF = cerebrospinal fluid; IADL = instrumental activities of daily living. Results represent Pearson correlation coefficient and p value.
Previous studies have compared participants with delirium to other people with similar illnesses or undergoing similar surgical procedures (6–8). Although this is also important, the clinical similarities and differences between delirium and dementia also need to be understood at a pathophysiological level. Additionally, delirium is frequently clinically confused with dementia by clinicians who are less familiar with these syndromes (1), so the identification of biochemical markers, which would facilitate a diagnostic test, is of the utmost importance because delirium is a medical emergency. More rapid identification of delirium would permit faster and more appropriate intervention and avoid the complications of misdiagnosis. Diagnostic tests would also assist with research. Further research is required to understand whether these changes are seen in older people with similar levels of acute illness but no delirium and are therefore simply a manifestation of acute illness rather than related to specific delirium pathophysiology.

Delirium results in deterioration of cognitive and activities of daily living function (1–4). Affected patients subsequently more often require increased assistance at home, placement in assisted living, or nursing home. This suggests that some process associated with delirium aggravates dementia and is different to the general course of dementia. Such differences may, hopefully, be identified by comparing people with dementia with people with delirium.
Although comparing markers in serum may be useful in identifying the differences between delirium and dementia, such an enterprise is more likely to be successful if the actual site of the pathology can be studied. Some may question the ethical aspects of studying patients who are unable to offer informed consent. However, there are clear pathways to obtain consent for such patients. To deny our patients the potential benefits of medical research are to condemn them to continue suffering in the same way.

We have identified a number of differences in CSF of patients with delirium compared with patients with Alzheimer’s dementia and raised lactate correlates best with the clinical manifestations of delirium. Lactate is a product of anaerobic glycolytic metabolism formed when pyruvate is reduced by lactate dehydrogenase in the absence of mitochondria, such as in erythrocytes or when oxidative metabolism is impaired, such as during ischaemia (20, 21). Elevated CSF lactate levels have been found to correlate with the severity of neuronal injury in traumatic brain injury (22).

In healthy participants who perform heavy exercise, no increase in CSF lactate levels are found, indicating that excess lactate arising from the periphery is taken up in healthy brains by neurons and metabolized (24). Hence, increased CSF lactate levels found in patients with delirium may also indicate an impairment of the lactate uptake or metabolism, although the lack of correlation with serum lactate in our study makes it more likely due to neuronal damage or a failure of aerobic metabolism, resulting in excess lactate arising from the CNS. We found no significant difference in mean serum lactate levels, although the delirium group’s serum lactate was 40% higher, mainly because of two participants with unusually high serum lactate, but the overall pattern suggests that serum lactate is mostly not the cause of elevated CSF lactate in delirium (Figure 1).

NSE is a glycolytic enzyme found only in cells of neuronal origin. Injury to neuronal tissue leads to elevated CSF NSE levels in ischaemic brain damage (25) stroke (26) and anoxic encephalopathy after cardiac arrest (27) and correlates with the extent of neuronal damage (28). In patients with Alzheimer’s and vascular dementia, CSF NSE levels are unchanged (29, 30), which suggests that the differences we observed were not due to elevated NSE levels in our control group who had dementia. Enolase is one of the CSF proteins more susceptible to oxidative stress and, once oxidized, is more readily degraded (31, 32).

Reduced cerebral glucose metabolism is a central feature of Alzheimer’s dementia and its detection by fluorodeoxyglucose positron emission tomography scanning is not only diagnostic but also correlates with and precedes the clinical stages (13). The changes in CSF glucose that we found are suggestive of an accelerated episode of glucose hypometabolism, most clearly seen in participants with worse outcomes where CSF glucose levels were lower, in addition to the effects on lactate and NSE, though in the overall group, there appears to be a spillover of glucose from the peripheral circulation. Correlation with fluorodeoxyglucose positron emission tomography scanning may help to clarify whether focal glucose hypometabolism accounts for the differential symptomatology seen in subgroups of patients with delirium.

The typical neuronal ischaemic pattern is of simultaneously elevated CSF lactate and NSE. In our study, lower CSF NSE and higher CSF lactate were found in the delirium group with a strong negative linear correlation, suggesting either a disruption of the glycolytic pathway with a switch from aerobic to anaerobic glucose metabolism by neuronal cells or suppression of glycolysis in neurons or the inability of neuronal cells to take up lactate released by astrocytes.
The stronger correlation between lactate and clinical indices for severity of delirium and outcome measurements suggests that lactate may be more central to the pathophysiology of delirium than NSE. Therefore, we suggest that increased CSF lactate induces the secondary suppression of NSE levels in neuronal cells, leading to a lower level detected in CSF. Our findings may support the disrupted astrocyte–neuron lactate shuttle hypothesis, which suggest that glutamate stimulation suppresses glycolysis in neurons in favor of lactate production by astrocytes to supply neuronal energy requirements (33), and glutamate has long been suspected to be of etiological significance in delirium (1,34). A lactate shuttle has also been postulated in skeletal muscle to explain findings of net lactate production, in the absence of hypoxia, during muscle activity. Lactate is a useful metabolic intermediate because it can be exchanged rapidly among tissue compartments (35).

We found no significant difference in S100B levels, whereas a recent study including 412 patients found a significantly increased median blood S100B during and after delirium in the order of 12% and 100%, which suggests that our findings may have been a Type II error as the differences in our groups’ median values were of a similar order (10). However, the pattern of markers and absence of any significant change in S100B levels does not exclude the possibility of cell death in delirium, and the metabolic changes identified suggest significant cellular dysfunction, which may eventually lead to neuronal loss. This level of metabolic derangement may well be associated with a degree of apoptosis.

We also found a 40% increase in CSF protein. CSF protein may be elevated in a range of CNS infections, intracerebral or subarachnoid haemorrhage, or head injury, from which none of our patients suffered. Recent work has identified an increase in blood chemokines in elective cardiac surgery patients with delirium, including C-C molif ligand-2, which mediates blood–brain barrier disruption and could thereby account for an increase in CSF protein (7).

Our study has some limitations in that it involves only small numbers of patients, and the delirium patients were not restricted to one diagnostic group. Additionally, we have taken a one-off snapshot of these patients’ biochemical findings, although we have collected subsequent clinical information. The patients were not randomized but were quite well matched on most baseline characteristics, apart from those who are affected by delirium and acute illness. Addition of a control group of nondemented nondelirious individuals would have enriched the study.

These metabolic findings may have important therapeutic implications for delirium and impact on its nonpharmacological management because of their link to clinical outcomes. High CSF lactate levels were associated with greater functional impairment, greater mortality, and more severe delirium. Future studies are required to elucidate the origin of the elevated CSF lactate and decreased NSE to better understand the pathogenesis of delirium and to define the implications for an increased risk of dementia.

Conflict of Interest
There are no actual or potential conflicts of interest.

Funding
This study was funded by an unrestricted grant from the Julia Lowy Foundation.

Acknowledgments
We would like to acknowledge the invaluable contribution of our patients and the assistance of the staff of Prince of Wales Hospital.

References


