CORRELATION BETWEEN SERUM LACTATE DEHYDROGENASE (LDH) AND SEIZURE – AN OBSERVATION IN CLINICAL CASES

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Abstract- Introduction
Serum lactate dehydrogenase (LDH) is an enzyme that catalyses the interconversion of lactate and pyruvate. LDH inhibition can reduce the excitability of neurons in mice; this leads to the hope that LDH inhibitor may be used to treat seizure. Translating this laboratory experimental finding to clinical medicine, one would like to investigate the potential correlation of serum LDH and seizure in human.

Objective
The objective of this study is to investigate “would a patient with an acute illness, who has seizure as one of the clinical manifestations, has an elevated serum LDH before, during, or after an episode of seizure?”

Method
The PubMed database was searched. The search algorithm was: (epileps* OR seizur*) AND (lactate dehydrogenase* OR LDH). Patients with known established conditions that could elevate LDH were excluded.

Results
Fifteen clinical cases met the criteria and were reviewed. Their serum LDH levels in relation to a seizure event were studied. The ratio of serum LDH to the upper limit of the reference ranges were all above 1.0 (ranging from 1.4 to 23.1).

Conclusion
Patients with an acute illness, who had seizure as one of their clinical manifestations, had elevated serum LDH above the upper limit, before, during, or after an episode of seizure.

I. INTRODUCTION
Serum lactate dehydrogenase (LDH) is an enzyme that catalyses the interconversion of lactate and pyruvate which is a product of glycolysis. LDH has been perceived as an indicator of disease and tissue injury[1]. For an example, it has been used as a diagnostic marker for cancers[2]. In addition, elevation of LDH can be caused by cardiac and pulmonary diseases (e.g. infarction, myocarditis, chronic heart failure, pulmonary embolism, pneumonia), megaloblastic anaemia, hepatitis, renal disease (e.g. infarction, transplant rejection), and autoimmune diseases (e.g. rheumatoid arthritis, vasculitis, dermatomyositis, and systemic sclerosis)[3].

Epilepsy is a prevalent condition affecting approximately 1% of the world’s population[1]. Researches in the quest for antiepileptic medications have been extensive in the past decades[1]. Recently, Sada and colleagues have investigated a seizure model in mice and reported that inhibiting LDH decreases the excitability of neurons. On the basis of their laboratory experiments, they have concluded that LDH-inhibitors are a promising group of antiepileptic medications[4]. The finding may shift the paradigm of a traditional view that epilepsy is a neuronal disease to a new perspective that epilepsy can be a metabolic disease because it can be treated by inhibiting LDH which is a metabolic enzyme[1]. Clinicians can investigate serum LDH level in the biochemistry test of their patients. Bearing in mind of the paradigm that seizure can be an activity that may have correlation with LDH, one would like to investigate a related clinical question i.e. “would a patient with an acute illness, who has seizure as one of the clinical manifestations, has an elevated serum LDH before, during, or after an episode of seizure?” The listing of causes for elevated serum LDH in a recent pathology handbook has no included seizure[3]. The objective of this article is to study the potential correlation between the serum LDH and seizure in human based on published clinical cases.

II. METHOD
The PubMed database was searched on 30th August 2015. The search algorithm was: (epileps* OR seizur*) AND (lactate dehydrogenase* OR LDH).

This study has included cases of patients with seizure in which a serum LDH level was reported. Nonetheless, patients with an established diagnosis of epilepsy, and patients who are taking an antiepileptic medication were excluded. Patients who have a malignancy were excluded because LDH is significantly associated with malignancy[2]. In addition, patients with the following known and established conditions that could cause an elevation in LDH were excluded: cardiac and pulmonary disease (e.g. myocardial infarction, myocarditis, chronic heart failure, pulmonary embolism, pneumonia), megaloblastic anaemia, hepatitis, chronic renal disease, and autoimmune disease (e.g. rheumatoid arthritis, vasculitis, dermatomyositis, and systemic sclerosis) [3]. The clinical cases were
reviewed. The main clinical features of the patients and the time-course sequence of the serum LDH in relation to a seizure event was extracted from the cases and reflected in Table 1. Ratio of the serum LDH to the upper limits were computed in order to standardize the readings for comparison purpose. A forest plot was constructed to show the ratio of the included cases.

III. RESULTS

The above search algorithm resulted in a total 232 articles in which 15 clinical cases met the criteria for this study. The cases of acute illnesses in which seizure was one of the clinical manifestations included carbon monoxide poisoning, rodenticide (strychnine) poisoning, overdose of tramadol, overdose of venlafaxine (an antidepressant medication), thrombotic microangiopathies preceded by pancreatitis, thrombotic microangiopathies preceded by fibrillar glomerulonephritis, thrombotic thrombocytopenia purpura following a streptococcal infection, HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet) with subdural haemorrhage, HELLP syndrome with eclampsia and antiphospholipid syndrome, active systemic lupus erythematosus (SLE), hypotension in secondary to adenovirus infection in twin boys, heat stroke, Rocky Mountain spotted fever, Reye syndrome, and Sturge-Webber syndrome (see Table 1).

The time-course of serum LDH in relation to a seizure event: six cases in which seizure occurred on admission had their serum LDH levels reported on admission, five cases had seizure during the course of hospitalisation and their serum LDH levels were reported on the day of their first seizure, and four cases did not specify the time-course event but reported the maximum LDH levels instead.

Six cases had the reference ranges of serum LDH included, while nine cases had not. With reference to the pathology handbook[3], the upper limits of serum LDH for individuals aged zero to 30 days, two to six years, and above 16 years were set at 600 U/L, 350 U/L, and 250 U/L respectively. The ratio of serum LDH to the upper limit of the reference ranges were all above 1.0 ranging from 1.4 to 23.1 (see Figure 1).

One of the authors of the clinical cases has provided a correlation of time-course correlation of the serum LDH in relation to a seizure event but the time-course correlation of the serum LDH and the onset of a seizure were not reported. Hence, the time-course correlation of the serum LDH and seizure could not be delineated. Furthermore, the scope of this review was limited to cases that had reported serum LDH in a patient with an acute illness who had seizure as one the clinical manifestations. Cases that had not reported a serum LDH were not reviewed.

Despite the limitations, this article may encourage clinicians to observe, use, and report serum LDH in their clinical cases when indicated. Reporting on the correlation of time-course of serum LDH in relation to seizure may help to characterise their potential correlation. With more clinicians contributing to case reports, we may create a larger database for further analysis in the future.

ACKNOWLEDGEMENT

I would like to thank Frances Guinness, Librarian at Bathurst & Orange Health Service Libraries at New South Wales, Australia, for her assistance in obtaining some relevant published articles cited in the references.

Figure 1 Patients with an acute illness, who had seizure as one of their clinical presentations, and their corresponding ratio of serum LDH to the upper limit
TMA: thrombotic microangiopathy; HELLP: haemolysis, elevated liver enzymes, and low platelet; SDH: subdural haemorrhage; APS: antiphospholipid syndrome; MAHA: microangiopathic haemolysis anemia; SLE: systemic lupus erythematosus; TTP: thrombotic thrombocytopenia purpura; URTI: upper respiratory tract infection

Note: The patient had a mild seizure on Day 56. The above graph was constructed using the original data provided by the first author who granted permission to include it in this article[5]

REFERENCES

### Table 1: Patients with an acute illness, who had seizure as one of the clinical presentations, and their corresponding serum LDH levels

<table>
<thead>
<tr>
<th>Case</th>
<th>The patient's clinical presentations &amp; diagnosis</th>
<th>Serum LDH level</th>
<th>Note</th>
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<tbody>
<tr>
<td>1</td>
<td>A 25-year-old Smith woman had severe carbon monoxide poisoning manifested by coma, status epilepticus, and cardiac arrest. She had placed a 150-mg fire at her bedside since midnight to warm her room. Her family members found her having a seizure and she was unconscious. [7].</td>
<td>On admission, her serum LDH = 459 U/L (reference ranges: 100 – 120 U/L).</td>
<td>Her serum glucose and routine serum electrolyte levels were normal. The results of urine toxology screening tests, including tests for benzodiazepines, amphetamines, and cannabinoids, opiates and cocaine, were negative [7].</td>
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<td>2</td>
<td>A 14-year-old woman presented with persistent vomiting, dizziness, bilateral visual loss, stroke-like episodes, epileptiform activities, slight (prognostication) angiomotor, cortical edema, and gliotic calcifications in the right central hemisphere, and thalamic injuries. She had Sturge-Weber syndrome. Her muscle and neurological disorders may be the result of thalamo-dysplasia due to excessive vasoreactivity, increased muscle stiffness, and decreased muscle tone since her childhood. [6].</td>
<td>On admission, her serum LDH = 1102 U/L (reference ranges: 34 – 250 U/L).</td>
<td>On admission, she was in a comatose state, accompanied by episodes of twitching that began on the left face, soon spread to the left limb [8].</td>
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<td>3</td>
<td>A 54-year-old man with fibrovascular dermatitis associated with thrombocytopenia and high levels of non-antigenic basement membrane antibody, presented with a high fever and amnesia. On hospital day 58, the patient had a mild seizure [5].</td>
<td>On admission, his serum LDH was elevated at 705 U/L on 4th day of admission, his serum LDH rose to 1253 U/L on 58th day when he had a mild seizure. His serum LDH was 252 U/L (reference range: 177 – 284 U/L) on 5th day of admission.</td>
<td>He had no noteworthy family history and was not taking any medications on a regular basis. The reference ranges were provided by the authors via an email to me [5].</td>
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<td>4</td>
<td>A 27-year-old Smith woman with pregnancy-induced hypertension was admitted for intermittent fever spikes. On day 3 of admission, she had her first generalized tonic-clonic seizure. The investigations showed no sign of infection but HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) and CT scan of her brain showed a right-sided intraparenchymal subdural hemorrhage with midline shift [9].</td>
<td>On day 23 when she had her first seizure, her serum LDH was elevated at 1314 U/L (4.2 times higher than 350 U/L upper limit) [9].</td>
<td>Lumbar puncture for cerebrospinal fluid analyses had not been done to exclude meningitis [9].</td>
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<td>5</td>
<td>A 29-year-old Korean pregnant woman (gestation 20 weeks) with antiphospholipid syndrome (APS) presented with persistent epigastric pain. She underwent cesarean delivery at 25 weeks gestation and she had a generalised tonic-clonic seizure before the cesarean delivery [10].</td>
<td>On admission, her serum LDH was elevated at 750 U/L on the day she had her first generalised tonic-clonic seizure, her serum LDH was 1424 U/L (3.6 times higher than 250 U/L upper limit) [10].</td>
<td>The patient had HELLP syndrome with echinococcus complicating APS [10].</td>
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<td>6</td>
<td>A 74-year-old man presented with acute epigastric pain who had acute pancreatitis presenting an acute episode of thrombocytopenia. 5 days after admission, he had a seizure [11].</td>
<td>On day 3 when he had a seizure, his serum LDH was elevated at 214 U/L (4.2 times the upper limit of 50 U/L) [11].</td>
<td>A brain CT indicated intracranial hemorrhage or infection [11].</td>
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<td>7</td>
<td>A 19-year-old man presented with tramadol overdose (400 mg) induced generalised tonic-clonic seizures [12].</td>
<td>Serum rise in serum LDH to a maximum of 2589 U/L (5.1 times the upper limit of 250 U/L) [12].</td>
<td>The patient did not have history of heart failure and intercurrent electrolyte disturbances and blood glucose [12].</td>
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<td>8</td>
<td>A 10-year-old female with active systemic lupus erythematosus (SLE) presented with thrombocytopenia and epistaxis. She had generalised bone fractures due to disseminated intravascular coagulation. Her twin brother presented with the similar symptoms and was treated accordingly [13].</td>
<td>On admission, her serum LDH was 59 U/L (upper limit – 250 U/L) e. 2.4 times higher than the upper limit [13].</td>
<td>The syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia were ruled out by low urine sodium and urine osmolality [13].</td>
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<tr>
<td>9</td>
<td>A six-week-old infant presented with a fever, decreased oral intake, and seizures. He had hypoglycemia probably attributed to disseminated intravascular coagulation. His two brothers presented with the similar symptoms and were treated accordingly [14].</td>
<td>During hospitalisation, his serum LDH was 576 U/L [14] (9.0 times of the upper limit of 600 U/L).</td>
<td>The syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia were ruled out by low urine sodium and urine osmolality [13].</td>
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Correlation Between Serum Lactate Dehydrogenase (LDH) And Seizure – An Observation In Clinical Cases
<table>
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<tr>
<th>Condition</th>
<th>Notes</th>
<th>Reference</th>
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<tbody>
<tr>
<td>10</td>
<td>A 16-year-old male presented with a high fever and rash following an upper respiratory tract infection. His symptoms included a fever, an erythematous maculopapular rash around the neck, thorax, upper abdomen and the right ankle, and he had several episodes of seizures. The seizure activity resolved 12 hours after the onset of fever and rash. His serum LDH was 5100 U/L (20.4 times the upper limit of 250 U/L) [15]. The patient was discharged after 2 days with no further seizures.</td>
<td>[14]</td>
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<tr>
<td>11</td>
<td>An 18-year-old female accidentally ingested an unknown amount of &quot;hot sauce&quot;. She presented with fevers, hyperventilation, vomiting, and a seizure. She was admitted to the hospital with a temperature of 39.5°C. Her serum LDH was 950 U/L (3.7 times the upper limit of 250 U/L) [17]. The patient was discharged after 3 days with no further seizures.</td>
<td>[16]</td>
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<td>12</td>
<td>A 22-year-old male ingested an unknown amount of &quot;hot sauce&quot; on the day before admission. He presented with loss of consciousness and a seizure. He was admitted to the hospital with a temperature of 39.8°C. His serum LDH was 1250 U/L (5 times the upper limit of 250 U/L) [17]. The patient was discharged after 5 days with no further seizures.</td>
<td>[16]</td>
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<tr>
<td>13</td>
<td>A 6-year-old male with cerebral palsy developed a fever and a rash after consuming &quot;hot sauce&quot;. He presented with a rash, a headache, and a temperature of 41 degrees C. His serum LDH was 2935 U/L (11.8 times the upper limit of 250 U/L) [18]. The patient was discharged after 2 days with no further seizures.</td>
<td>[17]</td>
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<tr>
<td>14</td>
<td>A 46-year-old man presented with Rocky Mountain spotted fever and a fever. His serum LDH was 2935 U/L (11.8 times the upper limit of 250 U/L) [18]. The patient was discharged after 5 days with no further seizures.</td>
<td>[19]</td>
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<tr>
<td>15</td>
<td>A 14-year-old male presented with a fever and upper respiratory tract infection. He was admitted to the hospital with a temperature of 39.8°C. His serum LDH was 5100 U/L (20.4 times the upper limit of 250 U/L) [15]. The patient was discharged after 3 days with no further seizures.</td>
<td>[16]</td>
</tr>
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</table>

Note: * In cases where the references ranges of serum LDH were not provided, its upper limit was determined by making reference to a pathology handbook; the upper limits of serum LDH for individuals aged zero to 30 days, two to six years, and above 16 years were set at 600 U/L, 350 U/L, and 250 U/L respectively[3].

U/L = IU/ L (International unit/ Litre).

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