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Clinical Study

# Elevation of serum lactate dehydrogenase at posterior reversible encephalopathy syndrome onset in chemotherapy-treated cancer patients

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ABSTRACT

The pathophysiology of posterior reversible encephalopathy syndrome (PRES) is incompletely understood; however, an underlying state of immune dysregulation and endothelial dysfunction has been proposed. We examined alterations of serum lactate dehydrogenase (LDH), a marker of endothelial dysfunction, relative to the development of PRES in patients receiving chemotherapy. A retrospective Institutional Review Board approved database of 88 PRES patients was examined. PRES diagnosis was confirmed by congruent clinical diagnosis and MRI. Clinical features at presentation were recorded. Serum LDH values were collected at three time points: prior to, at the time of, and following PRES diagnosis. Student's *t*-test was employed. LDH values were available during the course of treatment in 12 patients (nine women; mean age 57.8 years [range 33–75 years]). Chemotherapy-associated PRES patients were more likely to be normotensive (25%) *versus* the non-chemotherapy group (9%). LDH levels at the time of PRES diagnosis were higher than those before and after ($p = 0.0263$), with a mean difference of 114.8 international units/L. Mean time intervals between LDH measurement prior to and following PRES diagnosis were 44.8 days and 51.4 days, respectively. Mean elapsed time between last chemotherapy administration and PRES onset was 11.1 days. In conclusion, serum LDH, a marker of endothelial dysfunction, shows statistically significant elevation at the onset of PRES toxicity in cancer patients receiving chemotherapy. Our findings support a systemic process characterized by endothelial injury/dysfunction as a factor, if not the prime event, in the pathophysiology of PRES.



## 1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic process that occurs in the setting of systemic infection, transplantation, pregnancy, autoimmune disease, and malignancy, processes that involve activation of the immune system, with or without concurrent hypertension. Examination of the milieu in which PRES typically occurs, coupled with the significant minority of cases that occur in the absence of hypertension, has challenged the traditional notion of PRES as a direct result of hypertension exceeding auto-regulatory control. Instead, PRES is now thought to occur as a result of systemic endothelial dysfunction leading to altered vasoregulatory control, blood pressure lability, and cerebral hypoperfusion [1].

Various pharmaceuticals have been implicated as factors in the development of PRES including immune suppressant agents, such as cyclosporine and tacrolimus, and anti-cancer chemotherapeutics. In the case of tacrolimus, a direct toxic affect on the endothelium has been proposed [2]. The mechanism by which other pharmaceuticals initiate or propagate a physiologic cascade leading to PRES is less well known, however an increasing number of agents, including many anti-cancer chemotherapeutic agents, have been implicated in PRES development. In order to better understand the pathophysiologic basis of PRES, we examined serum levels of lactate dehydrogenase (LDH) relative to the onset of PRES during anti-neoplastic chemotherapy treatment in a retrospective series of PRES patients. We hypothesized that elevation of serum LDH, a marker of endothelial dysfunction, would coincide with the development of PRES.

## 2. Materials and methods

A database of PRES patients was compiled through an Institutional Review Board approved search of our electronic medical database from 2007 through 2012 using International Classification

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of Diseases version 9 codes encompassing a diagnosis of PRES. Included subjects had MRI of the brain consistent with PRES as verified by consensus of two subspecialty certified neuroradiologists and a clinical diagnosis of PRES within the electronic medical record.

Retrospectively collected data included pertinent medical history (predisposing factors for the development of PRES), current drugs/therapies, and serum LDH. Serum LDH values were obtained at three time points: prior to PRES development, at toxicity, and following resolution of symptoms. Clinical features at presentation including first reported blood pressure and symptomatology were obtained from the electronic record. Hypertension was classified according to criteria of the American Heart Association as systolic pressure $\geqslant$140 and/or diastolic pressure $\geqslant$90 mmHg [3]. Extreme hypertension was defined as systolic pressure $\geqslant$180 and/or diastolic pressure $\geqslant$110 mmHg. Student's *t*-test using SAS (SAS Institute Inc., Cary, NC, USA) was used to analyze the normal distribution of serum LDH measurement at the three recorded time points (prior to, at the time of, and following PRES diagnosis).

## 3. Results

Twenty (23%) of the 88 patients in our PRES database developed PRES while undergoing chemotherapeutic treatment for neoplastic disease (mean age 59.7 years; range 33–75; 17 women, three men). Malignancy type, demographic information, and chemotherapy treatment at the time of PRES diagnosis are included in Table 1. Of the 20 cancer patients, 12 (60%) were undergoing treatment for multiple myeloma.

Five of the chemotherapy patients (25%) were normotensive at the time of PRES diagnosis and eight (40%) exhibited extreme hypertension as classified by the American Heart Association criteria. In the remainder of the cohort, six patients (9%) were normotensive, 32 (49%) were hypertensive, and 28 (42%) had extreme hypertension at presentation. Two of the non-chemotherapy patients did not have recorded blood pressure at presentation. Seizure was the most common presentation, documented in 14 (70%) of the chemotherapy group. Additional or alternative presentations included altered mental status (six patients; 30%), headache (four patients; 20%), and vision changes (seven patients; 35%).

For 12 of the 20 patients, serum LDH values were available at all three time points. Of this subset, nine were female, with mean age of 57.8 years (range 33–75 years). Mean serum LDH (normal range 100–248 international units [IU]/L) at the time of PRES diagnosis was 319 IU/L (standard error 47) *versus* 210 IU/L (standard error 31) before PRES and 199 IU/L (standard error 25) following PRES resolution. Comparison of LDH at PRES toxicity with PRES at the other time points (Fig. 1) revealed a statistically significant mean difference of 114.8 IU/L ($p$ = 0.0263, t = 2.565). Mean time intervals between LDH measurement prior to and following PRES diagnosis were 44.8 days and 51.4 days, respectively. Mean elapsed time between last chemotherapy administration and PRES diagnosis was 11.1 days.

**Table 1**
Malignancy type, demographic information, and chemotherapy treatment at the time of posterior reversible encephalopathy syndrome diagnosis

| Malignancy | Age/ Sex | Drug(s) |
|---|---|---|
| Melanoma/NSCLC | 67/F | Cisplatin, etoposide |
| Ovarian carcinoma | 70/F | Bevacizumab, cyclophosphamide |
| MM (BMT) | 68/F | VDT, BEAM, cisplatin, sirolimus |
| MM | 53/M | VDT, sirolimus |
| MM | 51/F | VDT |
| MM (BMT) | 54/F | Carfilizomib, thalidomide, dexamethasone |
| MM (BMT) | 54/M | BEAM |
| Melanoma | 56/F | Ipilimumab |
| Sarcoma | 33/F | Isosfamide |
| MM | 64/F | VDT |
| Gastrointestinal stromal tumor | 67/F | Imatinib |
| MM (BMT);TTP | 61/F | Melphalan, rituximab |
| MM | 72/M | Adriamycin, bortezomib, cisplatin, thalidomide, temsirolimus |
| Melanoma | 48/F | Paclitaxel, paxopanib |
| MM | 75/F | Thalidomide, dexamethasone |
| MM | 60/F | Carfilzomib, thalidomide |
| MM (BMT) | 54/F | MVDTPACE |
| MM | 67/F | VDTPACE |
| Pancreatic adenocarcinoma | 67/F | gemcitabine |
| Rectal carcinoma | 53/F | Bevacizumab, FOLFOX |

NSCLC: non-small cell lung cancer; MM: multiple myeloma; BMT: allogeneic bone marrow transplant; VDT: bortezomib, doxorubicin, thalidomide; BEAM: carmustine, etoposide, cytarabine, melphalan; TTP: thrombotic thrombocytopenia purpura; MVDTPACE: melphalan, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; VDTPACE: bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; FOLFOX: folinic acid, fluorouracil, oxaliplatin.

## 4. Discussion

Investigation of the proposed immune basis of PRES pathophysiology is challenging given the lack of routine clinical sampling of biomarkers indicative of endothelial activation/dysfunction in this population. As such, hypotheses regarding PRES pathophysiology have been drawn in part from prior work in the realm of conditions such as preeclampsia/eclampsia that closely parallel PRES. Recent literature suggesting that the imaging manifestations of PRES are ubiquitous in eclamptic patients [4] supports such an approach, and we posit that the pathophysiologic phenomena leading to PRES likely parallel those that occur in eclampsia. Established evidence has linked the endothelial activation/injury that characterizes preeclampsia with a pro-inflammatory cytokine cascade, serum markers of endothelial injury, and elucidation of endothelial-derived vasoconstrictors such as endothelin-1 [5,6]. In these patients, endothelial activation is further exemplified by increased serum levels of fibronectin and von Willebrand factor, decreased production of nitric oxide and prostacyclin, increased production of thromboxane, and heightened reactivity to angiotensin II [6]. In sum, these factors contribute to an environment of vasoconstriction, as has

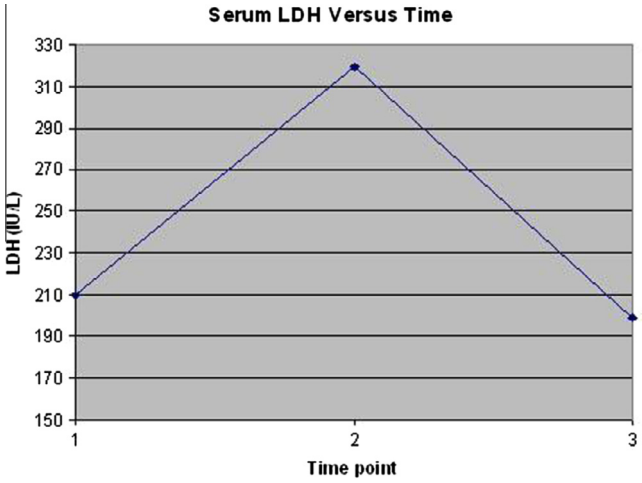


**Fig. 1.** Mean serum lactate dehydrogenase (y axis) at the three sampled time points (x axis): prior to posterior reversible encephalopathy syndrome (PRES) (1), at PRES diagnosis (2), and following PRES (3). IU = international units, LDH = lactate dehydrogenase.

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