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LACTIC ACIDOSIS AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A REVIEW OF THE LITERATURE

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ABSTRACT

Lactic acidosis is the most common cause of anion gap metabolic acidosis and is associated with high morbidity and mortality in hospitalized patients. The association between Hemophagocytic Lymphohistiocytosis (HLH) and lactic acidosis is still unclear. HLH causes cytokine overproduction which in turn induces lactic acidosis. There have been only few reports of type B lactic acidosis in HLH patients. There have been no studies addressing the outcome of cytokine removal for patients with HLH induced lactic acidosis. We reviewed literatures on HLH, focusing on its association with lactic acidosis and treatment options. This review demonstrates thatlactic acidosis in patients with HLH is under-recognized. Physicians should increase awareness of this association. In the setting of cytokine storm with multiorgan failure, cytokine removal with high blood flow, ultrafiltration rate and frequent membrane changes is a potential treatment option. More studies are urgently required to confirm this finding due to high morbidity and mortality of HLH.

Keyword: Lactic Acidosis, Hemophagocytic Lymphohistiocytosis, Cytokine Storm

1. INTRODUCTION

Lactic acidosis is the most common cause of anion gap metabolic acidosis in hospitalized patients (Madias, 1986). Increasing or persistently elevated lactate levels are associated with high morbidity and mortality (Bakker and Jansen, 2007). Tissue hypoperfusion in shock, leading to increased anaerobic metabolism, is responsible for type A lactic acidosis. In contradistinction, type B lactic acidosis occurs without evidence of systemic hypoperfusion. The etiologies of type B lactic acidosis include toxin-induced impairment of cellular metabolism, certain medications and malignancy (Warburg effect) (Warburg *et al*., 1927). D-lactic acidosis is an uncommon form of lactic acidosis that can occur in malabsorbed patients with short-bowel syndrome. **Table 1** demonstrates the causes of lactic acidosis.

1.1. Lactic Acidosis in Hemophagocytic Lymphohistiocytosis

Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation and overproduction of inflammatory cytokines. Even with the establishment of the treatment protocol for HLH, the survival rate for patients with HLH is only 54% with a median follow-up of six years (Henter *et al*., 2002; Trottestam *et al*., 2011). The association between HLH and lactic acidosis is still unclear. Although many studies have demonstrated that inflammatory cytokines can increase lactate production (Kiely *et al*., 2007; Nehar *et al*., 1997), there have been only few reports of lactic acidosis type B in HLH patients (DiCarlo *et al*., 2006; Hui *et al*., 2012; Jung *et al*., 2010). The outcome of cytokine removal for patients with HLH induced lactic acidosis has not been studied.

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Table 1. Causes of lactic acidosis

Causes of lactic acidosis
Type A
• Acute hypoxia
• Anemia
• Carbon monoxide poisoning
• Cardiogenic shock
• Hemorrhagic shock
• Septic shock
Type B
• Systemic disease
Liver failure
Malignancy
• Drugs or toxins
Metformin
Cyanide
Salicylate, ethylene glycol, methanol, Propylene glycol
Linezolid
Propofol
Stavudine, didanosine
Isoniazid
• Hereditary enzyme deficiency
D-lactic acidosis

Table 2. Reported cases of lactic acidosis in HLH

Case	Age (year)	Associated diseases	Complication	Lactate level	Treatment	Outcome
1 (DiCarlo *et al*., 2006)	10 yo male	-None	-Multiorganfailure -ARDS -AKI	Not available	-CVVHDF –IV etoposideand-Pulsemethylprednisolone	-Survived 2 weeks after-Died 2 months from systemic candidiasis
2 (DiCarlo *et al*., 2006)	10 yo male	-EBV–T -cellLymphoma	-Multiorganfailure -ARDS -AKI	3.5 mmol/L (31 mg/dL)	-CVVHDF IV-ganciclovir-Chemotherapy	-Off ventilator day 18. -Off CVVHDF (total 2 weeks) -Renal function recovered. -2 months of hospitalization.
3 (DiCarlo *et al*., 2006)	12 yo male	-EBV-(NK) cell Non-Hodgkin lymphoma	-Multiorgan failure-ARDS -AKI-Septic shock	2.4 mmol/L (22 mg/dL)	-CVVHDF-IV ganciclovir -Chemotherapy-Antibiotics	-Extubated for 3 weeks then again developed respiratory and cardiac failure and died.
4 (Hui *et al*., 2012)	34-day-old female	None	-Multiorganfailure -ARDS-AKI-Septic shock	15.4 mmol/L	-CAVH	-Off CRRT 48 h-85 days of hospitalization. -Underwent BM transplant-Had BM Transplant complications: Veno-occlusive disease, GVHD and superimposed sepsis and died 9 months afterpresentation.
5 (Jung *et al*., 2010)	79 yo male	-Diffuse large Bcell lymphoma	-Multiorganfailure -ARDS-AKI-Septic shock	10 mmol/L	-Intravenous methylprednisolone -Supportive treatment	-Died at day 3 after admission.

AKI = Acute Kidney Injury, ARDS = Acute Respiratory Distress Syndrome, CRRT = Continuous Renal Replacement Therapy, CAVH = Continuous Arteriovenous Hemofiltration, CVVHDF = Continuous Venovenoushemodiafiltration, EBV = Epstein-Barr Virus, NK Cells = Natural Killer Cells

Could HLH result in type B lactic acidosis? Our review of the literatures found only 5 cases describing lactic acidosis in HLH (**Table 2**) (DiCarlo *et al*., 2006; Hui *et al*., 2012; Jung *et al*., 2010).Two out of five cases (cases 1 and 4) had no diagnosis of malignancy; one of these cases (case 4) developed lactic acidosis prior to developing septic shock and multiorgan failure. Most cases with HLH associated lactic acidosis in the extant literature were diagnosed in childhood; there was only 1 case reported in adult (case 5), which described lactic acidosis in the setting of shock, so type A lactic acidosis could not completely be excluded.

HLH is an aggressive and life-threatening syndrome of excessive immune activation and overproduction of inflammatory cytokines. Studies have demonstrated that inflammatory cytokines can increase the activity of Lactate Dehydrogenase A (LDH-A) and inhibit Pyruvate Dehydrogenase (PDH) (Kiely *et al*., 2007; Nehar *et al*., 1997). The net effect is to increase production of lactate and could result in lactic acidosis. Conversely, lactic acidosis in HLH patients may reflect the status of cytokine production so that measurements of lactate levels may monitor HLH severity. The extreme overproduction of cytokines in HLH can result in cytokine storm, a severe condition that can cause multiorgan failure and high mortality and morbidity (Filipovich *et al*., 2010). Early diagnosis and treatment may prevent these patients from developing cytokine storm.

1.2. Potential Treatments for Lactic Acidosis in HLH in the Setting of Cytokine Storm

Patients with cytokine storm in HLH usually present with severe lactic acidosis and multiorgan failure requiring renal replacement therapy (Filipovich *et al*., 2010). Currently treatment of lactic acidosis is targeted on correcting the underlying causes and the consequent production of cytokines. Could cytokine removal help improve lactic acidosis? Evidence for cytokine removal in sepsis patients is controversial. So far, there is no evidence to support the use of Continuous Renal Replacement Therapy (CRRT) for cytokine removal in patients with sepsis. A study was discontinued after an interim analysis demonstrated more severe organ failure in the CRRT group (Payen *et al*., 2009). However, since patients with HLH-induced lactic acidosis and multiorgan failure are already treated with CRRT to maintain volume status and correct acid/base and electrolyte imbalance, we propose that it would be useful to investigate to what extent CRRT results in cytokine removal and thereby the reversal of lactate overproduction.

Studies have shown that optimal cytokine removal with CRRT could be achieved with a combination of a high blood flow, ultrafiltration rate and adsorption effect by frequent membrane changes (Bellomo *et al*., 1993; De Vriese *et al*., 1999). More studies are urgently required to confirm this finding due to high morbidity and mortality of HLH.

2. CONCLUSION

This review demonstrates that lactic acidosis in patients with HLH is under-recognized. Physicians should increase awareness of this association. In the setting of cytokine storm with multiorgan failure, cytokine removal with high blood flow, ultrafiltr ation rate and frequent membrane changes is a potential treatment option. More studies are urgently required to confirm this finding due to high morbidity and mortality of HLH.

2.1. Conflict of Interest Statement for all Authors

We do not have any financial or non-financial potential conflicts of interest.

2.2. Authors' Contributions

All authors had access to the data and a role in writing the manuscript.

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