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Warburg effect mimicking inborn errors of metabolism in childhood hematologic malignancies: A case-based systematic review

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Abstract

BACKGROUND

Type B lactic acidosis and hypoglycemia can occur in various pediatric conditions. In young children with a history of fasting preceding these metabolic derangements, inborn errors of metabolism should be primarily considered. However, the Warburg effect, a rare metabolic complication, can also manifest in children with hematologic malignancies. Only a few reports of this condition in children have been published in the literature.

AIM

To identify the clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis.

METHODS

We performed a comprehensive search of the PubMed, Scopus, and Cochrane databases without any time restriction but limited to English language articles. The databases were last accessed on July 1st, 2023.

RESULTS

A total of 20 publications were included in the analysis, all of which were case reports or case series. No higher quality evidence was available. Among children with hematologic malignancies and Warburg effect, there were 14 cases of acute lymphoblastic leukemia and 6 cases of non-Hodgkin's lymphoma including our illustrative case. Lactic acidosis occurred in 55% of newly diagnosed cases and 45% of relapsed cases. The mean age was 10.3 ± 4.5 years, and 80% of cases were male. The mean serum lactate was 16.9 ± 12.6 mmol/L, and 43.8% of the cases had concomitant hypoglycemia. Lactic acidosis initially subsided in 80% of patients

receiving chemotherapy compared to 60% in the contrast group. The mortality rate of newly diagnosed cases was 45.5%, while the relapsed cases represented a 100% mortality rate. All 8 patients reported before 2001 died from disease-related complications. However, patients described in reports published between 2003 and 2023 had a 54.5% rate of complete remission.

CONCLUSION

This complication has historically led to fatal outcome; however, patients who received chemotherapy showed a more favorable response. Therefore, it is crucial to promptly initiate specific treatment in this context.

Key Words: Warburg effect; Lactic acidosis type B; Inborn errors of metabolism; Leukemia; Lymphoma; Children

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Core Tip: In children with a history of fasting preceding lactic acidosis, inborn errors of metabolism (IEM) should be considered. However, we describe a case of 10-year-old boy with Burkitt leukemia who exhibited Warburg effect mimicking IEM. The most recent review on lactic acidosis in pediatric leukemia/lymphoma was published in the journal *Cancer* in 2001. All cases published to that date experienced worsening or recurrence of lactic acidosis, with a mortality rate of 100%. However, this updated systematic review has shown improved outcomes for children with this complication over the past two decades. Newly diagnosed patients and those who received chemotherapy displayed more favorable outcomes.

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INTRODUCTION

Leukemia and lymphoma are the most common childhood cancers worldwide[1]. These hematologic malignancies have been known to develop several complications, such as tumor lysis syndrome, hyperleukocytosis, and superior vena cava syndrome[2]. In terms of metabolic derangements, hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia commonly occur in patients with active disease. In a minority of cases, another form of metabolic complication in children with cancer is lactic acidosis[3].

Normal lactic acid production is mainly derived from glucose metabolism *via* the glycolytic pathway, and its utilization primarily occurs in the liver. When abnormal lactate accumulates in the body, it can lead to metabolic acidosis. A serum lactate between 2 mmol/L and 5 mmol/L represents hyperlactatemia, whereas lactic acidosis is commonly found when lactate levels are greater than 5 mmol/L[4]. Lactic acidosis usually occurs when there is an imbalance between oxygen delivery and oxygen demand in type A lactic acidosis. In contrast, type B lactic acidosis results from an impairment of oxidative phosphorylation, which is associated with various conditions, including inborn errors of metabolism (IEM), exposure to drugs toxins, and malignancies. The latter form, which is presented in patients with cancer, could be defined as the “Warburg effect”.

Unlike normal cells, which primarily rely on mitochondrial oxidative phosphorylation to generate the energy required for cellular processes, most cancer cells instead rely on aerobic glycolysis[5]. Various factors influence this phenomenon such as oncogene activation, loss of function of tumor suppressors, and effects of transcription factors[6]. This is a rare and unusual metabolic complication in children with hematologic malignancies. Few pediatric case series and case reports of this condition have been published. A previous literature review in 2001 showed that cases with lactic acidosis were more commonly observed in relapsed disease with specific clinical manifestations related to bone marrow, hepatosplenic, or lymph node involvement, and were associated with a poor outcome[3]. However, we encountered a case of newly diagnosed Burkitt leukemia in a 10-year-old boy with hypoglycemia and lactic acidosis which mimicked an IEM disorder. The patient achieved complete remission after treatment with a combination of rituximab and multiagent chemotherapy. Furthermore, we performed an updated systematic review in order to identify the overall profile of clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis from recent decades.

Illustrative case

A 10-year-old boy presented with poor appetite and vomiting that had persisted for 2 d. The physical examination did not show any masses, lymphadenopathy, or hepatosplenomegaly. Complete blood count and peripheral blood smear were within normal limits. A critical blood sample demonstrated the following values: Sodium of 142 mmol/L (normal range: 136-143 mmol/L); potassium of 4.0 mmol/L (normal range: 3.8-4.9 mmol/L); chloride of 109 mmol/L (normal range: 101-107 mmol/L); HCO₃ of 9 mmol/L (normal range: 17-26 mmol/L); anion gap of 24 mmol/L (normal range: 10-

14 mmol/L); blood urea nitrogen of 17 mg/dL (normal range: 7.3-21 mg/dL); creatinine of 1.1 mg/dL (normal range: 0.31-0.61 mg/dL); venous pH of 7.3 (normal range: 7.35-7.45); base excess of -15.2 mmol/L [normal range: (-2)-(+2) mmol/L]; and glucose of 49 mg/dL (normal range: 70-100 mg/dL). Further laboratory studies showed increased serum lactate (3.7 mmol/L; normal range: 1-2 mmol/L), serum ketone (2.7 mmol/L; normal range: 0-1 mmol/L), uric acid (12.5 mg/dL; normal range: 3.4-7.0 mg/dL), and triglycerides (354 mg/dL; normal range: 0-200 mg/dL), while serum cortisol and blood ammonia were normal (20.9 µg/dL and 50 µmol/L, respectively).

Based on the patient's clinical signs and symptoms, wide anion gap metabolic acidosis with ketotic hypoglycemia, IEM especially gluconeogenesis defects, glycogen storage disorders, and organic acidemia were considered. Subsequently, a specific test for plasma amino acids was performed, but only a nonspecific increase in cystathionine of 8.1 nmol/mL (normal range: 0-3 nmol/mL) and β-aminoisobutyric acid of 598.0 nmol/mL (normal range: 0-2 nmol/mL), which is a product of pyrimidine metabolism, was demonstrated. Urine organic acid testing showed an increased excretion of lactic acid and 4-hydroxyphenylactic acid. These findings explained that lactic acidosis was the cause of the wide anion gap metabolic acidosis without any supporting evidence of those IEM.

During admission, the patient developed hypertension and seizure. Computed tomography scan of the brain was performed, which revealed posterior reversible encephalopathy syndrome. The results of the metabolic workup showed that he had hyperuricemia, hyperphosphatemia, hypocalcemia, and acute kidney injury, along with markedly elevated levels of lactate dehydrogenase. These abnormal findings were consistent with tumor lysis syndrome.

Further computed tomography scan of the chest and abdomen was performed to evaluate the cause of hypertension and metabolic derangement, which demonstrated a posterior gastric wall thickening, and infiltrative soft tissue thickening of peritoneum and omentum without hepatic involvement. In addition, lobulated multifocal hypo-enhancing lesions were found scattered throughout the bilateral enlarged renal parenchyma. The patient underwent esophago-gastroduodenoscopy for gastric tissue biopsy, and histological pathology revealed a monotonous, intermediate-size lymphoid cells with starry sky appearance. These cells showed round nuclei with finely clumped chromatin and several paracentral nucleoli. Tingible body macrophages phagocytosing apoptotic debris were also observed. The immunohistochemistry testing was positive for CD20, CD79a, CD10, c-MYC, and Ki67 (> 95%), leading to the definitive diagnosis of Burkitt lymphoma.

After the procedure, the patient experienced disease progression characterized by progressive cytopenia with abnormal cells observed on peripheral blood smear. As part of disease staging, a bone marrow examination was performed, which revealed a lymphomatous involvement of 30%. The final diagnosis was Burkitt leukemia. A combination of rituximab and multiagent chemotherapy was administered following the St. Jude Mature B-Cell lymphoma and leukemia study III group c protocol. The patient responded well to the treatment, and the metabolic derangement was rapidly resolved. As of June 2023, the patient has been in complete remission for 1 year and 3 mo.

MATERIALS AND METHODS

Data sources and searches

Three authors (Permtawee K, Choed-Amphai C, and Chanthong S) independently conducted searches of the PubMed, Scopus, and Cochrane databases without any time restrictions. The following keywords were used for the search: "lactic acidosis"; "Warburg"; "pediatric"; "child"; "leukemia"; and "lymphoma". For PubMed, the specific search-term strategy was: ["acidosis, lactic" (MeSH Terms) or "acidosis" (All Fields) and "lactic" (All Fields) or "lactic acidosis" (All Fields) or "lactic" (All Fields) and "acidosis" (All Fields) or "warburg" (All Fields) or "warburg's" (All Fields)] and ["paediatrics" (All Fields) or "pediatrics" (MeSH Terms) or "pediatrics" (All Fields) or "paediatric" (All Fields) or "pediatric" (All Fields) or "child" (MeSH Terms) or "child" (All Fields) or "children" (All Fields) or "child's" (All Fields) or "children's" (All Fields)] and ["leukaemia" (All Fields) or "leukemia" (MeSH Terms) or "leukemia" (All Fields) or "leukaemias" (All Fields) or "leukemias" (All Fields) or "leukemia's" (All Fields) or ["lymphoma" (MeSH Terms) or "lymphoma" (All Fields) or "lymphomas" (All Fields) or "lymphoma's" (All Fields)] or ["haematologic malignancy" (All Fields) or "hematologic neoplasms" (MeSH Terms) or "hematologic" (All Fields) and "neoplasms" (All Fields) or "hematologic neoplasms" (All Fields) or "hematologic" (All Fields) and "malignancy" (All Fields) or "hematologic malignancy" (All Fields)]. Only articles published in English language were considered for selection.

Article selection

Inclusion criteria were as follows: Type B lactic acidosis in children with hematologic malignancies (including leukemia and lymphoma); and presence of data on clinical course, treatment strategies, and outcomes. Articles which did not meet these criteria were excluded. Summarization of the inclusion and exclusion criteria for this systematic review is presented in Table 1. The study followed the preferred reporting items for systematic reviews and meta-analysis 2020 guideline[7].

Data extraction

Extracted data included demographic and disease characteristics, laboratory parameters, clinical course, treatment strategies, and outcomes.

Data analysis

A qualitative systematic analysis was conducted using descriptive statistics. Due to differences among individual cases and small sample sizes, a meta-analysis could not be performed.

Table 1 Inclusion and exclusion criteria

Criteria
Inclusion
Children, 0 to 18 yr
Diagnosis of hematologic malignancy, including leukemia and lymphoma
Presence of lactic acidosis
Availability of clinical course, treatment, and outcome data
Exclusion
Adults, > 18 yr
Diagnosis of other solid tumors
Presence of other causes of metabolic acidosis without lactic acidosis
Incomplete information regarding clinical courses, treatment, and outcomes

RESULTS

Search results and article inclusion

A total of 115 publications were obtained through the search. Thirty-five abstracts were screened. The publications were limited to English language articles that provided detailed information about the clinical courses of type B lactic acidosis in children with leukemia or lymphoma resulting in the inclusion of 18 articles. A further two publications were discovered from manually searching the references of prior articles (Figure 1). The 20 included publications were case reports and case series, and there was no higher quality evidence available for this rare complication. These could be categorized into three groups according to cause of type B lactic acidosis, including Warburg effect, thiamine deficiency, and medications. Table 2 summarizes the clinical and laboratory parameters, treatments, and outcomes of the previously reported cases[3,8-26].

Demographic and disease characteristics

Among the pediatric cases with hematologic malignancies and the Warburg effect, there were 14 of acute lymphoblastic leukemia (ALL), including 7 with B-ALL, 4 with T-ALL, and 3 with unknown cell type, as well as 6 cases of non-Hodgkin's lymphoma (NHL), which consisted of 5 of Burkitt leukemia/lymphoma and 1 of T-NHL. Lactic acidosis occurred in 11 cases with newly diagnosed leukemia/lymphoma (55%), while the remaining cases had relapsed disease (45%). The mean age of the patients was 10.3 ± 4.5 years, and 80% of the cases were male.

Clinical manifestations and laboratory parameters

The most common clinical manifestations were dyspnea (44.4%), symptoms related to cytopenia (38.9%), fever (27.8%), weight loss (27.8%), and splenomegaly (27.8%). Hepatic involvement, which included patients with hepatomegaly, impaired hepatic synthetic function, cholestasis, or imaging-proven infiltrative disease, was found in 62.5% of cases (10 out of 16 patients). Renal involvement, which was defined as patients with imaging-proven infiltrative disease, occurred in about half of the cases (8 out of 14 patients). Patients with renal failure that might have resulted from other specific causes, such as tumor lysis syndrome, were excluded. The mean serum lactate was 16.9 ± 12.6 mmol/L, and 43.8% of the cases had concomitant hypoglycemia.

Treatment strategies

Almost all cases received sodium bicarbonate infusion (85%) in addition to general management protocols such as delivery of intravenous fluids and glucose. Renal replacement therapies, including continuous renal replacement therapy and peritoneal dialysis, were provided in only 20% of cases. Chemotherapy was given to three-quarters of the patients as a specific treatment.

Clinical courses and outcomes

Lactic acidosis initially subsided in about 80% of patients receiving chemotherapy compared to 60% in the contrast group. Furthermore, patients treated with chemotherapy had a more favorable response (complete remission of 40% vs 0%, respectively). The disease status may also affect the long-term outcome. The mortality rate of patients with newly diagnosed hematologic malignancies and lactic acidosis was 45.5%, while the relapsed patients had a 100% mortality rate. Warburg effect accounted for 23.1% of the causes of death. This review also highlighted that patients in the last two decades have experienced better outcomes than those in the previous review. Prior to 2001, patients diagnosed with leukemia or lymphoma-associated lactic acidosis had extremely poor outcomes. Six out of eight cases died from the disease-related conditions, while the other two cases experienced uncontrolled infections. However, publications between 2003 and 2023 revealed that 54.5% of cases achieved complete remission. In the minority of cases, patients with type B

Table 2 Demographics, treatments, and outcomes of previously reported children with leukemia/lymphoma and type B lactic acidosis

Ref.	Primary diagnosis	Age in yr, Sex	Clinical manifestation	Initial lactate in mmol/L	Blood glucose in mg/dL	Hepatic involvement	Renal involvement	Treatment	Clinical course	
									Lactic acidosis	Outcome
Type B lactic acidosis-Warburg effect										
Field <i>et al</i> [8]	Relapsed ALL	4, M	Bleeding, hepatosplenomegaly	20.2	NR	Yes	NR	Bicarbonate, radiotherapy, chemotherapy	Improved but recurred	Death from disease
	ALL	8, M	NR	9.9	NR	NR	NR	Bicarbonate, chemotherapy	Improved but recurred	Death from infection
Coleman <i>et al</i> [9]	Relapsed T-ALL	2, M	Lymphadenopathy, splenomegaly, dyspnea	24.6	74	No	NR	Bicarbonate, thiamine, insulin, methylglyoxal	Improved but recurred	Death from disease
Ali <i>et al</i> [10]	Relapsed B-ALL	12, M	Poor appetite, weight loss, abdominal pain	12.0	NR	No	Yes	Bicarbonate, chemotherapy	Improved but recurred	Death from infection
Révész <i>et al</i> [11]	Relapsed Burkitt lymphoma	8, M	Seizure, altered mental status, dyspnea, polydipsia, polyuria	24.0	93	No	Yes	Bicarbonate, thiamine, chemotherapy, radiotherapy	Improved but recurred	Death from disease
Sillos <i>et al</i> [3]	Relapsed T-ALL	11, F	Altered mental status	10.8	47	Yes	No	Bicarbonate, CRRT, chemotherapy	Improved but recurred	Death from disease
	Relapsed T-ALL	17, M	Altered mental status, dyspnea, edema	16.0	132	No	No	Bicarbonate	Worsened	Death from disease
	T-NHL	18, F	Fever, weight loss, lymphadenopathy, splenomegaly, dyspnea	15.4	44	Yes	No	Bicarbonate, chemotherapy	Resolved but recurred	Death from disease
Hayek and Srinivasan [12]	B-ALL	7, M	Anemia, lymphadenopathy, hepatosplenomegaly	8.4	96	Yes	Yes	Bicarbonate, PD, chemotherapy	Resolved after chemotherapy	CR
Rastogi <i>et al</i> [13]	Burkitt lymphoma, HIV	11, M	Fever, hepatosplenomegaly, periorbital and pedal edema	4.2	26	Yes	NR	Bicarbonate, glucagon	Improved	Death from disease
Luscri <i>et al</i> [14]	Relapsed B-ALL	7, M	Fever, ascites, dyspnea	5.5	33	Yes	NR	Bicarbonate, CRRT	Worsened	Death from LA, disease
Kulkarni <i>et al</i> [15]	Burkitt lymphoma	12, M	Dyspnea, hepatomegaly, abdominal pain	21.0	Normal	Yes	Yes	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Terpe <i>et al</i> [16]	B-ALL	11, M	Nausea, dyspnea, lymphadenopathy, abdominal pain, pancytopenia	21.0	48	Yes	Yes	Bicarbonate, chemotherapy	Worsened	Death from LA, ACS
Gökçe <i>et al</i> [17]	B-ALL	13, M	Weight loss, nausea, bone pain	62.0	97	Yes	Yes	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Schuh <i>et al</i> [18]	Relapsed B-ALL	12, M	Fever, abdominal pain, bicytopenia	14.8	80	Yes	Yes	Chemotherapy	Worsened	Death from disease
Narayani <i>et al</i> [19]	ALL	2, M	Fever, pancytopenia	13.5	96	NR	No	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
Khera <i>et al</i> [20]	T-ALL	11, F	Poor appetite, weight loss, nausea, dyspnea, bicytopenia	20.0	104	No	No	Bicarbonate, chemotherapy	Resolved after chemotherapy	CR
O'Rourke <i>et al</i> [21]	Burkitt leukemia	13, M	NR	NR	Low	NR	NR	Chemotherapy	Worsened	Death from LA

Hui <i>et al</i> [22]	Relapsed B-ALL	17, F	Poor appetite, weight loss, bicytopenia	15.0	NR	NR	No	Bicarbonate CRRT	Improved	NR
This study	Burkitt leukemia	10, M	Poor appetite, nausea, vomiting	3.7	49	No	Yes	Rituximab, chemotherapy	Resolved after chemotherapy	CR
Type B lactic acidosis-thiamine deficiency										
Oriot <i>et al</i> [23]	Relapsed ALL, on TPN without vitamin	3, M	Altered mental status, fever, dyspnea, hepatomegaly	30.0	43	Yes	No	Bicarbonate, PD, thiamine	Resolved	CR
Svahn <i>et al</i> [24]	B-ALL, on TPN without vitamin	0.9, F	Altered mental status	18.6	NR	NR	NR	Bicarbonate, multivitamin including thiamine	Resolved	CR
Didisheim <i>et al</i> [25]	ALL, post-sepsis	13, M	Fever, abdominal pain, hypotension	19.6	NR	NR	NR	ECMO, thiamine	Resolved	CR
Type B lactic acidosis-medication (s)										
Smolka <i>et al</i> [26]	Relapsed B-ALL, pneumonia (antibiotics including linezolid)	9, F	Altered mental status, dyspnea	19.0	NR	Yes	NR	Bicarbonate, withdraw linezolid	Improved	CR

ACS: Abdominal compartment syndrome; ALL: Acute lymphoblastic leukemia; CR: Complete response; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; F: Female; LA: Lactic acidosis; M: Male; NR: Not reported; PD: Peritoneal dialysis.

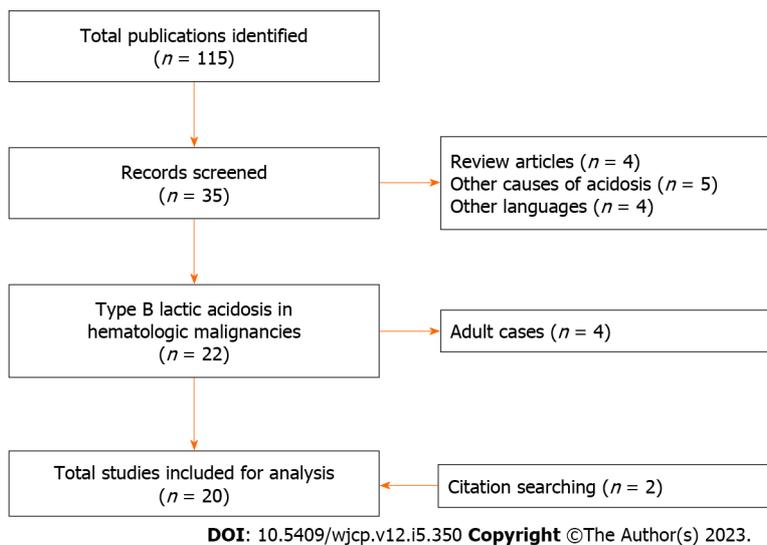


Figure 1 Preferred reporting items for systematic reviews and meta-analysis flowchart for study selection.

lactic acidosis from thiamine deficiency and linezolid treatment had excellent outcomes, with a 100% complete remission rate.

DISCUSSION

In the pediatric population, especially young children, an IEM disorder should be considered as a potential differential diagnosis in patients with a history of fasting or poor intake followed by hypoglycemia, and lactic acidosis with or without ketosis. The specific disorders of carbohydrate metabolism that can present with hyperlactatemia include glycogen storage diseases, gluconeogenesis defects, and organic acidemia. Findings from personal history taking, family history taking, and physical examination should be evaluated. Another crucial investigation in these diseases is a critical blood sampling taken during hypoglycemia episodes and including analysis of lactate, ammonia, blood gas analysis, insulin, cortisol, and ketones. Additional plasma amino acid and urine organic acid tests should be performed depending on the clinical suspicion [27,28]. After a comprehensive evaluation in our case, there was no evidence to support these

diseases. However, the patient later developed clinical symptoms of hypertensive emergency, tumor lysis syndrome and cytopenia, which led to the final diagnosis of Burkitt leukemia.

Type B lactic acidosis is an uncommon complication in patients with cancer, although there are several precipitating causes such as thiamine deficiency and medications. Cancer itself can lead to this form of metabolic acidosis. The proposed pathophysiology of this condition was first described by Warburg[29] in 1925. Since then, several studies have explored cancer metabolism and Warburg effect, which can be summarized into four main functions, as follows: Cell signaling; rapid adenosine triphosphate synthesis; biosynthesis; and tumor microenvironment[5]. Contrary to the publications on adult cases, the most recent review of lactic acidosis in pediatric leukemia and lymphoma was published in 2001 [3]. Sillos *et al*[3] summarized a total of 9 pediatric cases of hematologic malignancies with lactic acidosis, comprising 2 with lymphomas (1 Burkitt lymphoma and 1 T cell-non-Hodgkin's lymphoma) and 7 with ALLs. All cases experienced worsening or recurrence of lactic acidosis, and the outcome was extremely poor, with a 100% mortality rate. However, this updated review demonstrated that outcomes have improved in the last two decades, possibly due to increased understanding of disease pathophysiology, advances in treatment, and improvements in supportive care. Patients with newly diagnosed leukemia/lymphoma and those who received a specific treatment with chemotherapy appeared to have a better outcome. These findings also differ from those in the adult population. In the past decade, adults with hematologic malignancies who experienced lactic acidosis still had a mortality rate of more than 80%[30,31]. Despite the same pathophysiology of this complication in the pediatric and adult populations, disease status and response to treatment may explain the dismal outcome in adults. According to the United States' surveillance, epidemiology, and end results program database, survival rates according to age of diagnosis (all patients) at 17 years, 20 years, and 70 years were 75%, 48%, and 15%, respectively. Different treatment regimens and responses were determined to have played significant roles in this survival cliff drop-off[32]. This systematic review is limited by the rarity of this complication, with only a few case reports and case series available.

When compared to the other pediatric reports, our case presented with only nonspecific symptoms (a less common clinical manifestation). The patient had hypoglycemia with slightly elevated serum lactate levels, which is usually described as hyperlactatemia. However, further comprehensive investigations were performed and demonstrated that hyperlactatemia was the only remaining cause of the wide anion gap metabolic acidosis in this patient. One of the different management approaches used for this patient was administration of rituximab, a monoclonal antibody to CD20, which elicited a rapid response when combined with conventional chemotherapy. The lactic acidosis was abruptly resolved, and the patient has remained in complete remission.

CONCLUSION

Historically, Warburg effect in childhood hematologic malignancies has led to absolute fatal outcome, but over the past two decades about half of the cases have achieved complete remission. Specific treatment should be promptly initiated in this context. Furthermore, our case illustrates this uncommon metabolic derangement in childhood Burkitt leukemia. While IEM are one of the causes of metabolic acidosis in young children, Warburg effect in hematologic malignancies should also be considered in older children.

ARTICLE HIGHLIGHTS

Research background

Type B lactic acidosis is a rare metabolic complication in children with hematologic malignancies which can mimic inborn errors of metabolism (IEM). There have been few pediatric case series and case reports published on this specific condition. Moreover, the most recent review was conducted over two decades ago, in 2001.

Research motivation

The illustrative case of a 10-year-old boy with Burkitt leukemia who exhibited Warburg effect mimicking IEM was the basis of our systematic review. The previous review of this metabolic complication showed an extremely poor outcome. In recent years, however, advancements in cancer treatments may have led to the overall improvement in the clinical course.

Research objectives

To identify the clinical course, treatment strategies, and outcomes of childhood hematologic malignancies with type B lactic acidosis.

Research methods

We performed a comprehensive search of the PubMed, Scopus, and Cochrane databases without any time restrictions to identify children with leukemia/lymphoma and type B lactic acidosis. The publications considered for inclusion were limited to English language articles.

Research results

Lactic acidosis initially subsided in 80% of patients receiving chemotherapy compared to 60% in the contrast group. The mortality rate of newly diagnosed cases was 45.5%, while the relapsed cases had a 100% mortality rate. All 8 cases reported before 2001 died from disease-related complications, while cases reported between 2003 and 2023 showed a 54.5% rate of complete remission.

Research conclusions

Historically, this complication has led to fatal outcome; however, patients who received chemotherapy showed a more favorable response. Therefore, it is crucial to promptly initiate specific treatment in this context.

Research perspectives

This systematic review has revealed an improvement in the clinical course and outcomes compared to the past. Future studies in this context might include a larger scale of cases involving multicenter research. Retrospective study on prognostic factors or therapeutic research in the era of immunotherapy and targeted therapy could also be performed in this population.

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FOOTNOTES

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