Abstract

Leukemia is the most common malignancy in the pediatric population and Acute Lymphoblastic Leukemia (ALL) is the most common subtype. Great improvement has been made in the therapy approach in the past decades, so that it is essential to be aware of the possible early and late side effects. Transient hyperglycemia and diabetes occur often among the children receiving induction chemotherapy with glucocorticoids and L-asparaginase. Many studies have been performed, in order to investigate the pathophysiology, risk factors and possible approach of these side effects. Aim of this article is to resume the recent data concerning the pathogenesis, the effects and the possible therapy strategy of this disorder.

Keywords: ALL: Acute Lymphoblastic Leukemia

Introduction

Leukemia is one of the most common malignancies among children with ALL being the most common subtype. Leukemia may be defined as a neoplastic disease that begins in the bone marrow and results in high numbers of abnormal blood white cells. In 2012-2014 in the UK there was an average of 1756 new cases of cancer in children per year. The three most common subtypes were leukemia, brain tumors and lymphomas. Especially ALL accounts for around 78% of all leukemia diagnosed in children, peaking between 2 and 4 years of age [1-3]. In 2017 it is estimated that 15270 children and adolescents ages 0 to 19 years will be diagnosed with cancer and 1790 will die of the disease in the United States. Childhood cancer rates have been rising slightly for the past few decades [4]. ALL is curable in 80% to 85% of the patients. In 2007-2013, 83% of children who diagnosed with ALL before age 20 years survived at least 5 years [4].

Since improvement in survival of pediatric leukemia has been made, evaluation of possible side effects of treatment, as well as their early recognition and management are necessary. Aim of this review is to remind us once again the need to be aware of the possible risk of developing hyperglycemia and diabetes during the induction treatment of ALL. Transient hyperglycemia occurs in high prevalence during the induction phase of the treatment protocol of ALL in the pediatric population.

Previous Studies

Hyperglycemia and diabetes induced by chemotherapy occur in the range of 0.2% to 16% [5-7] (see table 1). Pui et al reported hyperglycemia in 9.7% of the pediatric ALL patients in the induction period of chemotherapy, after receiving prednisone and L-asparaginase [8]. Weiser et al documented an incidence of hyperglycemia in 37% of patients during induction chemotherapy [9]. According to Pastrone et al 50% of ALL children may develop hyperglycemia, whereas Banihashem et al reported that 27.5% of the pediatric patients showed either diabetes mellitus or hyperglycemia [10]. Baillargeon et al reported transient hyperglycemia in 11% of hispanic children with ALL [11].
Results

Medication-induced diabetes in children with ALL during induction treatment may result in some cases in diabetic ketoacidosis [17] and may also be a risk factor for future impaired glucose tolerance and an early marker for metabolic disturbances later in life [18].

Several studies examined the risk factors for the development of hyperglycemia and diabetes in children treated for ALL. Baillargeon et al. documented that both age and body mass index are positively associated with the risk of hyperglycemia and females exhibited a higher risk than males [11]. Lo-was et al. showed that, overweight and higher age (>10 years old) are significant risk factors, but they found no gender difference [19]. Furthermore, the use of native L-asparaginase was associated with hyperglycemia, but the use of prednisolone instead of dexamethasone showed no difference. In contrast Banihashem et al reported that, preschool age was a predictor of hyperglycemia and that BMI had no significant influence in the development of hyperglycemia[10]. Gatzioura et al. reported that, fasting glucose levels on the eighth day of treatment, when higher than 110 mg/dl, are associated with a higher risk of developing transient hyperglycemia during the therapy protocol [20].

Discussion

The most common malignancy of children is leukemia accounting for around 30% of all cases with ALL being the most common type. There is an improvement over the last years in survival of pediatric leukemia so that evaluation and reassessment of the possible side effects of treatment is of great importance. Hyperglycemia occurs commonly in the pediatric population receiving induction chemotherapy, but a combination of glucocorticoids and L-asparaginase may cause diabetes mellitus. Physicians should be aware of these risk factors and perform an early and careful screening for hyperglycemia (fasting glucose levels) during the treatment of the patients with ALL.

Furthermore, application of the right treatment for hyperglycemia, such as insulin, permits an early clinical and biochemical normalization and enforces thereby the continuation of the chemotherapy. The use of insulin may reduce the period of hyperglycemia and therefore the possible future metabolic side effects.

Conclusions

Clinicians should be aware of the risk of hyperglycemia especially when an additional insulin defect or another additional risk factor, such as obesity or positive family history, are present. Future investigations of pediatric cohorts are needed to evaluate the influence and outcome of transient hyperglycemia as well as diabetes mellitus for long-term survival and metabolic syndrome.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Percentage of children developing hyperglycemia or diabetes</th>
<th>Medicaments who are mentioned in the study</th>
<th>Year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banihashem et al</td>
<td>27,5 %</td>
<td>L-asparaginase, Glucocorticoids, Vincristine, +/- Doxorubicin</td>
<td>2014</td>
</tr>
<tr>
<td>Baillargeon et al</td>
<td>11 %</td>
<td>L-asparaginase, Glucocorticoids, Vincristine, +/- Doxorubicin</td>
<td>2005</td>
</tr>
<tr>
<td>Weiser et al</td>
<td>37 %</td>
<td>Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, Methotrexate</td>
<td>2004</td>
</tr>
<tr>
<td>Pastore et al</td>
<td>50 %</td>
<td>L-asparaginase</td>
<td>1984</td>
</tr>
<tr>
<td>Pui et al</td>
<td>9,7 %</td>
<td>L-asparaginase, Prednisone</td>
<td>1981</td>
</tr>
</tbody>
</table>

Table 1: Summary of previous studies

There is a complex pathophysiology mechanism that explains the development of hyperglycemia in the pediatric population receiving induction chemotherapy. DeFronzo et al. have described a series of events that lead to genesis of diabetes as follow: 1) some patients showed a predisposition to enhance insulin resistance and propensity for β-cells failure, 2) specific risk factors such as preexisting obesity reinforce these defects, 3) diabetes mellitus comes up, when a concomitant insulin secretory defect is present, regardless of the etiology [12].

During the standard treatment of ALL, children receive 3 drugs in the first month of the therapy [4]. These include L-asparaginase, Vincristine and steroids as prednisolone. Children in high risk group of ALL receive a fourth chemotherapy drug, mostly daunorubicin. Additionally intrathecal chemotherapy using commonly methotrexate is performed. During the standard treatment of ALL, children receive 3 drugs in the first month of the therapy [4]. These include L-asparaginase, Vincristine and steroids as prednisolone. Children in high risk group of ALL receive a fourth chemotherapy drug, mostly daunorubicin. Additionally intrathecal chemotherapy using commonly methotrexate is performed. L-asparaginase inhibits insulin protein synthesis [14]. L-asparaginase may directly reduce the glucose-stimulated release of insulin from β-cells and indirectly reduce insulin production by causing pancreatitis. Furthermore, it is known, that corticosteroids induce insulin resistance. These effects may lead to the development of diabetes mellitus in children receiving chemotherapy, and more often in those with additional risk factors [5,14-16]. Additionally great importance lies in the disturbance of insulin receptors and abnormal response of α and β-cells to stimulate impulses [5,14] Pastore et al [14] concluded that, there was no significant difference in the serum glucose level before and after L-asparaginase treatment, suggesting an accumulative effect of drug dosage.
References


