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Published in:
PLoS ONE

DOI:
10.1371/journal.pone.0039523

2012

Link to publication

Citation for published version (APA):

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Co-Morbidity between Early-Onset Leukemia and Type 1 Diabetes – Suggestive of a Shared Viral Etiology?

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Abstract

Background: Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are common early-onset malignancies. Their causes are largely unknown but infectious etiology has been implicated. Type 1 diabetes (T1D) is an autoimmune disease for which infectious triggers of disease onset have been sought and increasing pointing to enteroviruses. Based on our previous results on co-morbidity between leukemia and T1D, we updated the Swedish dataset and focused on early onset leukemias in patients who had been hospitalized for T1D, comparing to those not hospitalized for T1D.

Methods and Findings: Standardized incidence ratios (SIRs) were calculated for leukemia in 24,052 patients hospitalized for T1D covering years 1964 through 2008. T1D patients were included if hospitalized before age 21 years. Practically all Swedish children and adolescents with T1D are hospitalized at the start of insulin treatment. SIR for ALL was 8.30 (N = 18, 95% confidence interval 4.91–13.14) when diagnosed at age 10 to 20 years after hospitalization for T1D and it was 3.51 (13, 1.86–6.02) before hospitalization for T1D. The SIR for ALL was 19.85 (N = 33, 13.74–27.76) and that for AML was 25.28 (8, 10.80–50.06) when the leukemias were diagnosed within the year of T1D hospitalization. The SIRs increased to 38.97 (26, 25.43–57.18) and 40.11 (8, 17.13–79.42) when T1D was diagnosed between ages 10 to 20 years. No consistent time-dependent changes were found in leukemia risk.

Conclusion: A shared infectious etiology could be a plausible explanation to the observed co-morbidity. Other possible contributing factors could be insulin therapy or T1D related metabolic disturbances.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. The underlying causes are largely unknown beyond ionizing radiation and the recently detected susceptibility genes [1,2,3]. However, an infectious etiology has been strongly implicated but the agents have evaded identification [4,5,6,7,8]. Acute myeloid leukemia (AML) is an adult disease but a few percent of cases occur in the childhood [9]. Viruses, solvents, ionizing radiation and smoking have been implicated in adults but the causes of childhood cases are unknown [9]. Type 1 diabetes mellitus (T1D) is an early-onset autoimmune disease in which immune response is directed against the insulin-producing beta cells of the pancreas, resulting in insulin-dependence. The autoimmune process is thought to be triggered in susceptible individuals by unknown factors [10,11]. T1D is increasingly thought to have a viral basis, probably a consequence through genetically determined aberrant response to an enteroviral infection [12,13]. Enterovirus RNA has been demonstrated in the blood and pancreatic tissue of early onset T1D patients [12]. Family history is an important risk factor for T1D for which the HLA region is the most important contributor [13,14,15]. The HLA locus regulates the response to many viral infections and even other T1D susceptibility loci are relevant to antiviral actions, including the IFIH1 gene modulating innate immunity [12]. Recently, genetic variation around the gene encoding IKZF1, a regulator of lymphocyte development and immune homeostasis, has been shown to confer susceptibility to both childhood ALL and T1D [1,16]. Previous epidemiological studies have shown significant correlations in incidence between ALL and T1D at both the international and regional level, with potential but unproven links with an infectious etiology [17,18]. In a previous study of cancer risk in T1D patients, we reported increased risk of leukemia, stomach and skin cancers [19]. In view of the increasing data on the possible viral etiology of T1D, we updated the Swedish dataset and investigated in detail the associations of early-onset leukemia with T1D.

Methods

The analyses were carried out by linking T1D patients (N = 24,052) from the nation-wide Hospital Discharge Registry (years 1964 to 2008) with cancer data from the Swedish Cancer Registry, collected in the Family-Cancer Database (1964 to 2006).
Results

The study was approved by the ethics committee at Lund University.

Table 1. SIRs for leukemia in T1DM patients according to age at leukemia diagnosis.

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>Age at diagnostic for leukemia (years)</th>
<th>&lt;10</th>
<th>10 - 20</th>
<th>21 - 50</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>SIR</td>
<td>95% CI</td>
<td>O</td>
</tr>
<tr>
<td>Leukemia diagnosed after hospitalization for T1D</td>
<td>ALL</td>
<td>3</td>
<td>2.31</td>
<td>0.43</td>
<td>6.83</td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td>0</td>
<td>0</td>
<td>3.97*</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>0</td>
<td>3</td>
<td>3.97</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>CML</td>
<td>0</td>
<td>0</td>
<td>3.97</td>
<td>0.76</td>
</tr>
<tr>
<td>Leukemia diagnosed before hospitalization for T1D</td>
<td>ALL</td>
<td>10</td>
<td>1.60</td>
<td>0.76</td>
<td>2.94</td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td>0</td>
<td>0</td>
<td>3.97</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>2</td>
<td>2.33</td>
<td>0.22</td>
<td>8.58</td>
</tr>
<tr>
<td></td>
<td>CML</td>
<td>0</td>
<td>0</td>
<td>3.97</td>
<td>0.76</td>
</tr>
<tr>
<td>Leukemia diagnosed before or after hospitalization for T1D</td>
<td>ALL</td>
<td>13</td>
<td>1.72</td>
<td>0.91</td>
<td>2.95</td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td>0</td>
<td>0</td>
<td>3.97</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>2</td>
<td>2.33</td>
<td>0.22</td>
<td>8.58</td>
</tr>
<tr>
<td></td>
<td>CML</td>
<td>0</td>
<td>0</td>
<td>3.97</td>
<td>0.76</td>
</tr>
</tbody>
</table>

O, observed; SIR, standardized incidence ratio; CI, confidence interval; *P < 0.05, **P < 0.01.

Case numbers in the reference population ALL: 1733 (<10 y), 701 (10–20 y), 562 (21–50 y), 2996 (total); CLL: 55 (<10 y), 15 (10–20 y), 728 (21–50 y), 798 (total); AML: 301 (<10 y), 296 (10–20 y), 1506 (21–50 y), 2103 (total); CML: 88 (<10 y), 93 (10–20 y), 1201 (21–50 y), 1382 (total).

doi:10.1371/journal.pone.0039523.t001
hospitalized for T1D before age 10, the only significant increase of 5.85 was for ALL diagnosed within one year \( (N = 7, 95\% CI 2.49–11.27) \), before or after T1D hospitalization \( (\text{data not shown}) \).

According to Table 2, the majority of T1D hospitalizations and leukemia diagnoses coincided with the same year. The mean calendar time difference between the two events depended however on the age at T1D hospitalization. For ‘leukemia diagnosed before or after hospitalization for T1D’ the median time difference was only 0.8 years for ALL and 0.7 year for AML, in the most common leukemia diagnostic group of 10 to 20 years. For leukemias diagnosed <10 years the mean difference was 3.5 years for ALL and 9.0 years for AML; for leukemias diagnosed between 21 and 50 years the mean difference was 13.8 years for ALL and 18.5 years for AML.

Table 2. SIRs for leukemia in T1D patients according to time at hospitalization for T1D and age at T1D diagnosis.

<table>
<thead>
<tr>
<th>Leukemia (T1D diagnosis at age 10–20 years)</th>
<th>Time at hospitalization for T1D (years)</th>
<th>(&lt;1\text{ year})</th>
<th>(\geq 1\text{ year})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(O)</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Leukemia diagnosed after hospitalization for T1D</td>
<td>ALL</td>
<td>15</td>
<td>28.59**</td>
</tr>
<tr>
<td></td>
<td>ALL (T1D 10-20 y)</td>
<td>14</td>
<td>72.87**</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>3</td>
<td>28.50**</td>
</tr>
<tr>
<td></td>
<td>AML (T1D 10-20 y)</td>
<td>3</td>
<td>43.27**</td>
</tr>
<tr>
<td>Leukemia diagnosed before hospitalization for T1D</td>
<td>ALL</td>
<td>18</td>
<td>15.99**</td>
</tr>
<tr>
<td></td>
<td>ALL (T1D 10-20 y)</td>
<td>12</td>
<td>25.26**</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>5</td>
<td>23.68</td>
</tr>
<tr>
<td></td>
<td>AML (T1D 10-20 y)</td>
<td>5</td>
<td>38.42</td>
</tr>
<tr>
<td>Leukemia diagnosed before OR after hospitalization for T1D</td>
<td>ALL</td>
<td>33</td>
<td>19.85**</td>
</tr>
<tr>
<td></td>
<td>ALL (T1D 10-20 y)</td>
<td>26</td>
<td>38.97**</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>8</td>
<td>25.28**</td>
</tr>
<tr>
<td></td>
<td>AML (T1D 10-20 y)</td>
<td>8</td>
<td>40.11**</td>
</tr>
</tbody>
</table>

O, observed; SIR, standardized incidence ratio; CI, confidence interval; 
*\(P<0.05\), **\(P<0.01\).

doi:10.1371/journal.pone.0039523.t002
Discussion

Outside therapeutic settings and exclusive of Down syndrome and co-twin affected with ALL, the present risks for ALL and AML are remarkably high [22,23]. For example, the analysis of sibship size as a proxy of infectious etiology showed an effect for ALL but not for AML yet the overall risk was only 1.3 (4 or more siblings vs. 1) but it increased 2.1-fold in those diagnosed below age 6 years [6]. Clearly, the present high risks require explanation, particularly as the hospitalized T1D population is not a small subgroup of all patients but practically all Swedish children and adolescents diagnosed with T1D, hospitalized at the start of insulin treatment [20]. There was also an indication that CLL, with a very different age distribution compared to T1D, might be related to T1D but with 3 cases the evidence awaits further confirmation. The main limitation of the present study is that it is purely epidemiological, lacking any data on serological analysis, but, at the same token, the diagnostic data on leukemia and T1D should be highly reliable [21,24]. Demanding virological proof for the present study appears overwhelming because conclusive proof has yet been obtained neither for ALL nor T1D, in spite of numerous attempts [4,7,11].

Our findings provide strong evidence for a relationship between early-onset leukemia risk and T1D. While it is possible that insulin therapy causes leukemigenesis directly through its growth-promotion effects, risks were also increased prior to first hospitalization for T1D. It is possible, although unlikely, that the high glucose levels and metabolic disturbance before the start of insulin therapy might trigger leukemia, in an analogous fashion to the increased risk of cancer associated with type 2 diabetes [25]. As the length of time to achieve stable glucose control (number of hospitalizations is a proxy for labile glucose levels) was not correlated with risk, this strongly argues against such an explanation. Furthermore, there was no evidence of a time trends, which should exclude strong environmental or treatment-related changes, assuming that the control of glucose levels has improved with time. Shared symptoms of generalized weakness and fatigue for childhood leukemia and T1D may contribute to the coincident detection, but there is no reason to doubt diagnostic accuracy. Whether autoimmunity itself would trigger leukemia is also a theoretical but not a likely option because it would not explain the coincident diagnosis of the two diseases and the decreasing leukemia risk past age 20 years. Finally by exclusion, our findings coupled with epidemiological and other data provide support for a common infective basis for the observed co-morbidity, which most probably could be viral in origin. It is not clear at what ages pancreatic tissue would be most vulnerable to viral damage but high positivity for enteroviral capsid proteins have been found in pancreatic islets in 72 patients with a mean age of 13 years, well within the present age range [26]. As genetic susceptibility to T1D and ALL is now well established an aberrant response to viral challenge leading to both diseases would provide an attractive basis for the observed co-morbidity.

Author Contributions

Conceived and designed the experiments: KH. Performed the experiments: RH KS. Analyzed the data: XS. Contributed reagents/materials/analysis tools: JS. Wrote the paper: KH.

References