Tampereen yliopisto

Henri Rosti

CO-OCCURRENCE OF ACUTE LEUKEMIA AND TYPE 1 DIABETES AMONG CHILDREN

A detailed case-series

Lääketieteen ja terveysteknologian tiedekunta
Syventävä opinnäytetyö
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TIIVISTELMÄ

Henri Rosti: Co-occurrence of acute leukemia and type 1 diabetes among children: A detailed case-series
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Leukemia on yleisin alle 15-vuotiaiden lasten syöpäsairaus, ja sen aiheuttajia ei täysin tunneta. Tyypin 1 diabetes (T1DM) on puolestaan yksi lasten yleisimmistä autoimmuunisairauksisa Suomessa. Aiemmat tutkimukset ovat viitanneet mahdolliseen yhteyteen akuutin leukemian ja T1DM:n välillä, mutta yhteyden selittäviä tekijöitä ei tunneta. Tutkimuksen tarkoituksena oli tunnistaa mahdollisia uusia tekijöitä, jotka olisivat voineet vaikuttavat sairauksien yhteisesiintymiseen. Tutkimus toteutettiin Tampereen yliopistollisessa sairaalassa (TAYS) tarkastelemalla potilaskertomuksia.

Potilaat tunnistettiin ICD-10 koodien avulla sairaalan tietokannasta tiedonhaun ammattilaisten toimesta, ja tutkimukseen valittiin mukaan potilaat, joilla oli sekä leukemia että T1DM. Edellytettiin myös, että tutkimushenkilöiden kumpikin diagnoosi oli asetettu ennen 18 vuoden ikää. Useimmilla tutkimushenkilöillä leukemia todettiin ennen diabetesta, ja osalla T1DM:n puhkeaminen liittyi asparaginaasi-hoidon aiheuttamaan haimatulehdukseen. Toisaalta osalla potilaista T1DM todettiin ennen leukemiaa, mikä viittaa siihen, ettei yhteys selity pelkästään leukemiahoitojen vaikutuksilla. Tutkimus vahvistaa jo olemassa olevaa tietoa leukemian ja T1DM:n yhteisesiintyvyydestä, mutta sen avulla löydettiin myös mahdollisesti uusi selittävä tekijä – Sotosin syndrooma – näiden sairauksien yhteisesiintyvyydelle.

Avainsanat: Leukemia, Tyypin 1 diabetes mellitus, lastentaudit

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Abstract

Background: Leukemia is the most common malignancy in children, while type 1 diabetes mellitus (T1DM) is one of the most prevalent autoimmune diseases among children. The etiology of both conditions is still largely unexplained, yet emerging evidence suggests a potential association between them. In this case-series we sought new potential factors behind the co-occurrence of leukemia and T1DM by thoroughly reviewing the medical records of patients diagnosed with both diseases.

Methods: We conducted a retrospective case series at Tampere University Hospital, Finland, identifying pediatric patients diagnosed with both acute leukemia and T1DM from 1990 to 2023 using ICD-10 codes. Clinical and laboratory data, including leukemia subtype, age at diagnosis, treatments, comorbidities, and medical history, were collected, reviewed and analyzed descriptively. Study protocol was locally approved, and health data privacy was respected.

Results: Among 12 initially identified cases, seven met the inclusion criteria. Five cases were diagnosed with B-cell acute lymphoblastic leukemia (B-ALL), one with T-ALL, and one with acute myeloid leukemia (AML). The mean age at leukemia diagnosis was 8.7 years (range from 0.7 to 15.3), while the mean age at T1DM diagnosis was 11.8 years (range from 7.5 to 17.8). In five cases, leukemia preceded T1DM, with two cases linked to asparaginase-induced pancreatitis. In two cases, T1DM developed before leukemia. Additional comorbidities included Down syndrome, Sotos syndrome, celiac disease, epilepsy, and Sweet's syndrome.

Conclusion: This case-series presents findings, which align with previous observations (e.g., Down syndrome, pancreatitis), but also suggest a potential new contributing factor (Sotos syndrome).

Background

Leukemia is the most common malignancy among children under 15 years of age with acute lymphoblastic leukemia (ALL) being the most common type (85%) followed by acute myeloid leukemia (AML, 10-15%). Leukemia is also the fourth most common cause of death among children.[1]

Incidence of type 1 diabetes mellitus (T1DM) in Finland is one of the highest globally, and T1DM is one of the most common AI diseases among children.[1,2] From 2015 to 2018, the incidence rate of T1DM in Finland among children under the age of 15 was 52.2 per 100,000 while the worldwide rate was 15 per 100 000 people.[2]

The exact etiologies of both acute leukemia and T1DM remain largely unexplained. Treatment of ALL by asparaginase can lead to drug-induced diabetes mellitus (DIDM) via severe pancreatitis. Also, corticosteroids can cause temporary hyperglycemia necessitating insulin treatment. Down syndrome patients are predisposed to both acute leukemia and T1DM[3]. Nevertheless, when accounting for these factors, there is emerging evidence that occurrence of T1DM is still significantly associated with acute leukemia, and what underlies this remaining association is currently unknown.[1,4–6]

To better understand the connection between T1DM and acute leukemia, we carefully reviewed all available medical charts of patients diagnosed with both diseases in our tertiary children's hospital. Our purpose was to explore if patient medical records would hold information that could help in explaining the co-occurrence.

METHODS

This case-series was conducted at the children's and adolescents' hospital in TAYS, Tampere, Finland. The cases from 1990 to 2023 were identified by the hospital's IT department using ICD-10 diagnosis codes, and the subjects were required to be under 18 years old at the timepoints both diagnoses were placed. The following clinical and laboratory data were collected and tabulated from the medical charts: age at both diagnoses, genetics and phenotypic subtype of leukemia, all treatments for both diseases, and every other comorbidity the subjects had. Data on growth, development and social history was also collected.

The data was analyzed descriptively, and the study was conducted following ethical standards of our hospital district, with health data privacy maintained and identifying information excluded at the analysis stage. The study protocol was approved by the chief medical officer of the hospital services division, wellbeing services county of Pirkanmaa.

RESULTS

Query to the hospital medical registry initially identified 12 individuals with both leukemia and T1DM. However, five cases were excluded after further inspection: one subject had type 2 diabetes mellitus, one had no data available due to moving to other area and one subject had only transient hyperglycemia without a confirmed diagnosis of T1DM. Moreover, two cases did not have leukemia.

In total, seven cases with both diseases were identified (Figure 1). Five out of seven cases were diagnosed with B-ALL: one *Pax5alt* subtype, one *TCF3-PBX1* subtype, while the rest did not have subtype information available. In addition, one case of T-ALL and one AML (M7) were identified. The mean age at leukemia diagnosis was 8.7 (range 0.7 to 15.3), while the mean age at diabetes diagnosis was 11.8 (range 7.5 to 17.8).

Out of six cases with ALL, five had a leukemia diagnosis preceding the onset of T1DM, with the time difference between diagnoses ranging from +0.5 to +9.8 years. Two cases developed T1DM following acute pancreatitis caused by asparaginase treatment, whereas two cases were diagnosed with T1DM 5.3 (B-ALL) or 6.8 (B-ALL) years after leukemia diagnosis and had no obvious connection to leukemia treatment. Two cases with either a T-ALL or B-ALL had T1DM diagnosis prior to leukemia diagnosis (-0.2 and -3.0 years, respectively). The only case with AML had T1DM diagnosed 9.8 years after leukemia diagnosis.

Additionally, the subjects suffered from few other medical conditions such as Down syndrome, celiac disease, Sotos syndrome, epilepsy, migraine, polycystic ovary syndrome and Sweet’s syndrome (Table 1).

Figure 1. Time difference between leukemia and T1DM diagnoses.

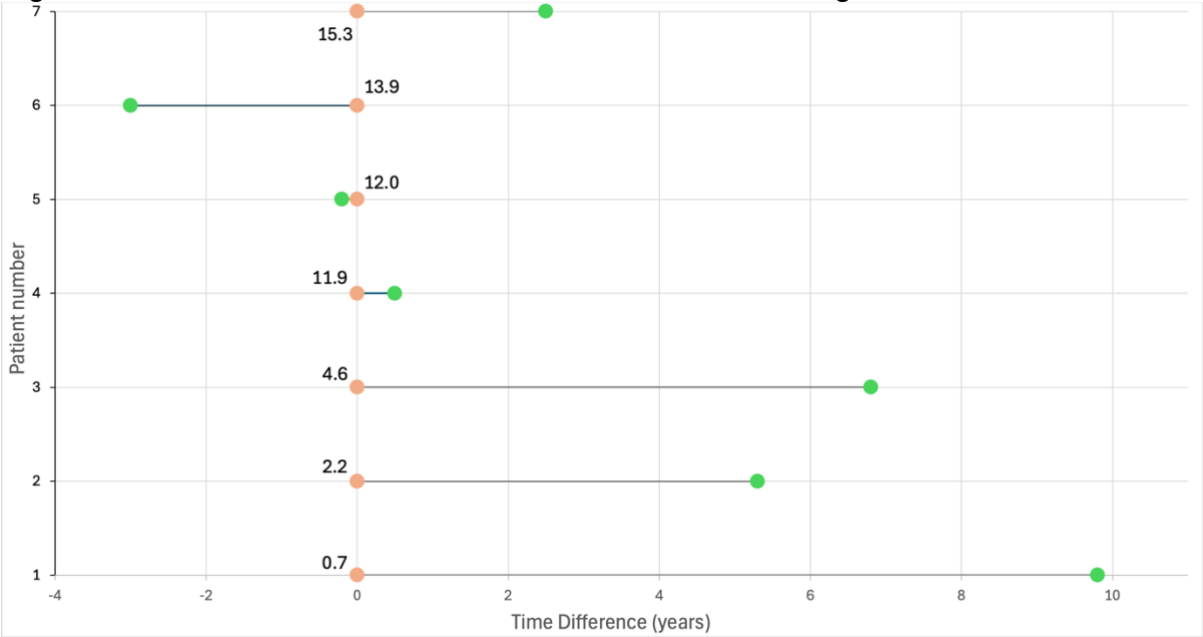

Figure 1 Orange dot represents patient's age at the moment of leukemia diagnosis and green dot represents the time difference between leukemia and T1D diagnoses. Numbers next to the orange dots presents the leukemia diagnosis ages.

Table 1. Patients' clinical characteristics.

ID	Sex	Leuk dx age (yrs)	Leuk subtype	Spesific subtype	T1DM dx age (yrs)	Identified cause of diabetes	Time difference[1]	Other conditions
1	Male	0.7	AML	M7	10.5		+9.8	Sotos syndrome, epilepsy
2	Male	2.2	B-ALL	Other	7.5		+5.3	
3	Female	4.6	B-ALL	Other	11.4		+6.8	Polycystic ovary syndrome
4	Male	11.9	B-ALL	Pax5alt	12.4	Pancreatitis	+0.5	
5	Female	12.0	B-ALL	Other	11.8		-0.2	Down syndrome, Celiac disease
6	Female	13.9	T-ALL	Other	10.9		-3.0	Sweet's syndrome, Migraine
7	Male	15.3	B-ALL	TCF3-PBX1	17.8	Pancreatitis	+2.5	

1. Age at T1DM diagnosis – Age at leukemia diagnosis

DISCUSSION

The co-occurrence of T1DM and childhood acute leukemia has been repeatedly documented.[1] In this case series, we aimed to provide a detailed account of the clinical sequence of events and to reveal potential factors behind the association by going carefully through individual patient's medical records. The number of cases with co-occurrence of both diseases was small in our hospital, and the study was not designed to determine whether the diseases occur together more often than expected. Nevertheless, we were able to identify known risk factors (pancreatitis and Down syndrome) as well as previously unrecognized factors (Sotos syndrome) potentially associated with co-occurrence. Notably, two cases were diagnosed with T1DM before leukemia, and two additional cases received a T1DM diagnosis years after completing leukemia treatment, further corroborating previous epidemiological research.[5,6]

For two subjects, T1DM was thought to be caused by pancreatitis, which was induced by asparaginase, leading to permanent insulin dependency. Of note, one of the patients who had T1DM prior leukemia, had also Down syndrome, a known risk factor for both conditions.[3]

While Down syndrome is a well-known risk factor for both leukemia and diabetes, other rare syndromes such as Sotos syndrome may also influence the occurrence of these diseases. Sotos syndrome is known to predispose to leukemia and could explain the occurrence of leukemia for that particular patient but its association with T1DM is still not clear, even though it has parallels to glucose metabolism.[3,8]

Additionally, Sweet syndrome was identified in an AML patient. Sweet syndrome is a rare inflammatory condition associated with malignancies and may not directly contribute to leukemia nor diabetes pathogenesis[7].

Our study also highlights the limitations of hospital registry queries. Our initial hospital registry search identified 12 patients, but five of them did not meet the study inclusion criteria. This underscores the shortcomings of hospital registries and encourages to review the query results by hand if possible.

In summary, with this case series, we identified several well-known risk factors for leukemia and T1DM, including Down syndrome and asparaginase-induced pancreatitis. Yet we discovered a new potential factor (Sotos syndrome) that could contribute to the association between T1DM and ALL.

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