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Early infection with cytomegalovirus and risk of childhood hematological malignancies

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Abstract

Background: Congenital cytomegalovirus (CMV) infection was recently identified as a risk factor for childhood acute lymphocytic leukemia by detecting the presence of CMV sequences in neonatal blood spots. In the current study, we asked whether *clinically apparent* CMV infection could be identified prior to hematological malignancy, using high quality Swedish population-based registries.

Methods: CMV infection was identified with appropriate ICD-9 or ICD-10 codes in the Patient and Medical Birth Registries, and childhood malignancies below the age of 15 were identified in the Cancer Registry, among 2,782,507 children born in Sweden 1987 to 2014.

Results: Observing all CMV infections registered earlier than 6 months prior to malignancy diagnosis, an increased hazard ratio (HR) of CMV-related infections, adjusting for congenital malformations, deformations, and chromosome abnormalities, was detected for hematological malignancies (HR=11.2, 95%CI: 5.8–21.5) but not for central nervous system tumors.

Conclusions: Higher CMV incidence was detected for children ostensibly exposed through maternal CMV infection during pregnancy with the index child.

Impact: The data are compatible with a congenital infection of CMV leading to increased risk of childhood hematological malignancies, but not tumors of the central nervous system, although a cautious interpretation is warranted because of the small numbers.

Introduction

A primary etiologic factor for pediatric acute lymphoblastic leukemia (ALL) appears to be patterns of infection during childhood. Exposure to infections via childhood contacts appears to decrease risk (1), while recurring and fulminant infections may increase risk (2, 3). It is unclear whether maternal infections during pregnancy affect risk but a recent report

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that examines viral sequences only strongly implicates congenital cytomegalovirus (CMV) playing a role (4).

CMV is also a suspected etiologic factor in adult glioma (5). Pediatric brain cancers have not received the same attention as adults, but recent reports support a high frequency of CMV in pediatric medulloblastoma and glioma (6, 7).

Congenital CMV infection as an etiologic agent for childhood cancers, if true, may find corollaries documented within population-based data. While most congenital CMV infections will go clinically undetected, a higher rate of clinical infection during pregnancy or in early life in children who contract cancer would support an etiologic role for CMV. We used high quality population based linked registries from Sweden (Medical Birth Registry, the Patient Registry, and Cancer Registry) to evaluate whether clinical indications for CMV infection could be detectable among mothers and/or their children who later contracted leukemia or brain tumors.

Materials and Methods

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2011/634-31/4, 2016/27-32, 2018/1257-32). We conducted a population-based cohort study including all children born in Sweden 1987–2014 identified through the nationwide Medical Birth Registry (MBR), where the identity of the biological mother could be confirmed in the Swedish Multigeneration Registry (n=2,916,314). The MBR records information from pregnancy and the perinatal period for both the child and mother. Children who migrated out of Sweden before their 15th birthday (2.8%) and children of the same sex from multiple births (1.8%, due to potential errors in matching specific individuals within same sex twins between registries) were excluded, leaving 2,782,507 children for analyses. The cohort was followed in the population registry, the Cancer registry, and the Cause of Death registry until the occurrence of a hematological malignancy or a central nervous system (CNS) tumor, death, their 15th birthday or end of study on 31st December 2015. Outcomes were classified using the International Classification of Diseases version 9 (ICD-9), hematological malignancies (ICD-9: 200–208) and CNS tumors (ICD-9: 191.0–192.9, morphology codes 9380–9481).

Cytomegalovirus and other infections were identified through linkage of the cohort and their mothers to the nationwide patient registry (registers all hospitalizations and from 2001 also outpatient specialist care was included), and from information in the MBR, with the following International Classification of Diseases Codes (ICD-10: B25, O35.3, P35.1 or ICD-9: 484.1, 078.5, 655.3, 771.1). Congenital infections at birth, apart from CMV, were identified using P35.0, P35.2, P35.3, P35.8, P35.9 or 771.0).

We compared the incidence rates of hematological malignancies or CNS tumors among CMV exposed children to those unexposed using Cox proportional hazard models with attained age as time scale with time of observation beginning at birth. Hazard ratios (HR) with 95% Confidence Intervals (CI) were estimated. Any and all indication of cytomegalovirus from the Patient Registry prior to 6 months before diagnosis of malignancy

(any diagnosis in either registry), or in the MBR only (meaning CMV infection during pregnancy) were identified. Age-specific analyses to assess whether CMV related effects differed by age or by tumor subtype (with age as a proxy) were conducted where attained age during follow-up was categorized into ages 0, 1–4, 5–9, and 10–14. Statistical analyses were conducted using STATA version 14.2 (College Station, TX, USA).

Results

In 31.3 million person years of observation 2,265 cases of hematological malignancies and 933 nervous system tumors were identified. Five children were diagnosed with both a hematological malignancy and a tumor in the nervous system. One hundred-eight children diagnosed with a hematological malignancy had a cytomegalovirus infection recorded in the Medical Birth Register 1987–2014 or the Patient Register 1987–2015; only 9 of these children had the cytomegalovirus infection six months or more before the diagnosis of the hematological malignancy or recorded in the MBR, and were therefore considered exposed. The remaining 99 children were considered to be uninfected with regards to the current analyses.

The HR of hematological malignancy among children exposed to any reported CMV infection was 12.10, 95% CI: 6.29–23.28 (Table 1). When adjusting for several clinical indications that may lead to an order for a CMV test – congenital malformations, deformations, chromosome abnormalities, and small or large for gestational age status – the HR was not appreciably affected (HR=11.34, 95% CI: 5.89–21.83). Stratification by age at diagnosis indicated a significantly higher HR among the youngest children: those children diagnosed at less than 1 year of age (adjusted HR=28.43, 95% CI: 7.03–115.0) and years 1–4, (adjusted HR=10.06, 95% CI: 3.76–26.86) (Table 1). Significant hazard ratios were also observed for the oldest age group (10–14 yrs) but not for the 5–9 year category (Table 1). To establish more specificity with regards to timing of infection, the MBR was examined further, where 3 of the infections were recorded. Despite these minimal numbers, significant HRs were demonstrated for CMV detected during pregnancy or at birth, indicating prenatal infection (adjusted HR=13.50; 95% CI: 3.37–54.03, Table 1). Childhood CNS tumors were analyzed in a similar fashion. Only one child was diagnosed with CMV 6 months or more prior to a brain tumor out of the 933 children identified (0.11%), compared to 1,037 children being diagnosed with CMV out of a population of 2,781,470 without CNS tumors (0.037%). This one individual was within the age at diagnosis category “1–4 years old” when there were 351 other cases without a history of CMV. There were with no reports of CMV during pregnancy or at birth among the 933 children with CNS tumors.

We also assessed whether other congenital infections (apart from CMV) at birth were associated with hematologic malignancy. A congenital infection was detected in 43,634 children in the Medical Birth Register or in the Patient Register. Of these children, 350 had congenital CMV, and 43,284 children had congenital infections other than CMV (mostly bacterial infections). Of these 43,284 children, 36 (0.083%) had a hematological malignancy and of the remaining 2,736,958 children 2,229 (0.081%) had a hematological malignancy. Cox proportional hazard ratio for having congenital infections, *excluding CMV* is 0.96 (95% CI: 0.69 – 1.34). Apart from the 350 diagnosed CMV infections, there were only 216 non-

CMV *viral* infections diagnosed congenitally, a frequency that was too low to calculate non-CMV viral risk ratios.

Discussion

CMV was not considered a potential causative virus for childhood leukemia until a recent report found evidence of CMV within pre-B cell ALL tumor cells commonly at diagnosis, pinpointed the *timing* of CMV infection as important, namely that the virus is detectable more commonly at birth in neonatal blood spots from children who were later diagnosed with ALL compared with controls (4). Our current results are compatible with this observation; we found a 12-fold higher incidence rate of hematological malignancies among children of mothers recorded with a CMV infection at delivery of the child. What was clearly different between the Francis *et al.* report (4) and the current data is the reported incidence of CMV in both the control and diseased population. CMV is a ubiquitous virus worldwide, but is usually asymptomatic. Universal *active* population screening of congenital CMV estimates a 0.5–2% incidence in western countries [about 0.5% in Sweden (8, 9)] and up to 6–14% in third world countries with viral culture or molecular methods (10). *Passive* screening in the Swedish population using registry-based methods in our current analysis indicates a *clinically-identified* prevalence of CMV at birth of 0.0066% in non-cases and 0.088% in children who later were diagnosed with a hematologic malignancy. The vast majority of CMV infections are not detected or recorded in the registries used here – but those that are indicate a greater than 10-fold higher incidence of a hematological malignancy early in life, mirroring the molecular data shown previously (4). Since CMV screening occurs prior to hematological malignancy diagnosis, we have no reason to believe in a differential detection bias between the children who contracted a hematological malignancy compared to those that did not. We cannot rule out the possibility that the likelihood of being tested for CMV is related to some other risk factor for childhood hematological malignancy. However, adjustment for known risk factors which may prompt a CMV test did not change our findings. We also assessed potential impact from other congenital infections and found no associations with hematologic malignancy, supporting specificity for CMV in the risk of childhood ALL.

Weaknesses of the current study include the low sample size of children with cancer and CMV, providing unstable risk estimates based on only a few exposed cases. Pregnant women and neonates are not routinely checked for CMV infection. Given that the exposures were recorded prior to the childhood cancer diagnoses, these errors would bias the findings towards the null. If, however, it is the maternal symptoms of CMV infection themselves that are associated with an increased risk of childhood malignancies, such as fever and/or impaired immune function, our findings may not be unique to CMV infection, but our analysis of other infections give no evidence towards this scenario. It is difficult to distinguish CMV as a bystander of maternal immune suppression or causal agent from this epidemiologic association analysis alone; undoubtedly more research and confirmatory studies are required given the implications on cancer prevention that could be afforded by vaccination for CMV.

Infectious diseases have long been suspected to play a role in childhood cancers, but specific agents were not previously identified in leukemias or brain tumors [reviewed in 11]]. Less clear is the role of maternal infections during pregnancy. A recent review counted 11 studies detecting increased risk from maternal infections to influenza, pneumonia, chickenpox, herpes zoster, lower genital tract infection, skin disease, sexually transmitted diseases, Epstein-Barr virus (EBV), and *Helicobacter pylori* but without any consensus infections, and CMV-related illnesses were not reported (12). Many epidemiologic studies of rare diseases like childhood cancer are impeded by retrospective recall bias as they use case-control design dependent on questionnaires and not data generated prior to the index disease such as the current cohort study.

Mathematical evidence supports the role of an *in utero* transforming event for leukemia, thought to be viral (13). Such a virus, envisions M. Smith in 1997, should “induce genetic instability, have specific effects on B (not T) lymphocytes, have higher rates of infection in regions with lower socioeconomic status, limited oncogenic potential, produce minimal symptoms in the primary infection, and have the ability to cross the placenta without causing fetal abnormalities” (13). Apart from its capacity to produce fetal abnormalities, CMV fulfills these viral activities and in addition has protein products capable of affecting all aspects of the hallmarks of cancer (14). Indeed, the prenatal nature of the CMV infection here coincides with the known timing of the prenatal genetic mutations that are known to precede leukemia (15). Establishing a role for this virus in childhood cancer identifies a primary target for surveillance, intervention and/or prevention.

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Incidence rate ratios and hazard ratios for hematological malignancies among children exposed to CMV infection compared to unexposed children, Sweden 1987–2014

Table 1.

	Person-years		Persons		No. cases		CMV vs. no CMV		
	No CMV	CMV	No CMV	CMV	No CMV	CMV	HR ^{M1} (95% CI)	HR ^{M2} (95% CI)	HR ^{M3} (95% CI)
Overall *	31 331 956	10 181	2 781 470	1 037	2 256	9	12.1 [6.3,23.3]	11.2 [5.8,21.5]	11.3 [5.9,21.8]
Stratified by age group									
0	2 770 062	998	2 781 470	1 037	177	2	31.3 [7.8,126]	27.7 [6.9,112]	28.4 [7.0,115]
1–4	10 211 144	3 485	2 771 224	977	1 085	4	10.8 [4.0,28.8]	9.7 [3.6,25.9]	10.1 [3.8,26.9]
5–9	10 381 997	3 319	2 336 804	766	602	1	5.2 [0.7,36.9]	5.0 [0.7,35.3]	4.9 [0.7,35.2]
10–14	7 968 753	2 379	1 824 140	566	392	2	17.1 [4.3,68.7]	16.3 [4.1,65.4]	16.3 [4.0,65.3]
Medical Birth Registry †									
CMV child	31 340 318	1 819	2 782 323	184	2 263	2	15.2 [3.8,60.9]	13.5 [3.4,53.9]	13.5 [3.4,54.0]
CMV mother	31 341 102	1 035	2 782 419	88	2 264	1	13.5 [1.9,96.0]	13.5 [1.9,96.0]	13.6 [1.9,96.5]
CMV child and/or mother	31 339 310	2 827	2 782 239	268	2 262	3	14.8 [4.8,45.9]	13.7 [4.4,42.6]	13.8 [4.4,42.8]

* Child CMV infection earlier than 6 month prior to diagnosis or maternal CMV during pregnancy

† CMV infection identified from the Medical Birth Registry at birth

M1: Model 1. Cox proportional hazard ratio with attained age as time scale

M2: Model 2. Model 1 adjusted for congenital malformations, deformations and chromosomal abnormalities registered in the medical birth register (ICD10 Q00-Q99, ICD9 740–759)

M3: Model 3. Model 2 adjusted for small, and large for gestational age