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Raquel da Rocha Paiva Maia [I]

Victor Wünsch Filho [II]

Infection and childhood leukemia: review of evidence

Infecção e leucemia infantil: revisão das evidências

ABSTRACT

OBJECTIVE: To analyze studies that evaluated the role of infections as well as indirect measures of exposure to infection in the risk of childhood leukemia, particularly acute lymphoblastic leukemia.

METHODS: A search in Medline, Lilacs, and SciELO scientific publication databases initially using the descriptors "childhood leukemia" and "infection" and later searching for the words "childhood leukemia" and "maternal infection or disease" or "breastfeeding" or "daycare attendance" or "vaccination" resulted in 62 publications that met the following inclusion criteria: subject aged ≤ 15 years; specific analysis of cases diagnosed with acute lymphoblastic leukemia or total leukemia; exposure assessment of mothers' or infants' to infections (or proxy of infection), and risk of leukemia.

RESULTS: Overall, 23 studies that assessed infections in children support the hypothesis that occurrence of infection during early childhood reduces the risk of leukemia, but there are disagreements within and between studies. The evaluation of exposure to infection by indirect measures showed evidence of reduced risk of leukemia associated mainly with daycare attendance. More than 50.0% of the 16 studies that assessed maternal exposure to infection observed increased risk of leukemia associated with episodes of influenza, pneumonia, chickenpox, herpes zoster, lower genital tract infection, skin disease, sexually transmitted diseases, Epstein-Barr virus, and *Helicobacter pylori*.

CONCLUSIONS: Although no specific infectious agent has been identified, scientific evidence suggests that exposure to infections has some effect on childhood leukemia etiology.

DESCRIPTORS: Children. Leukemia, etiology. Causality. Infection. Review.

[I] Programa de Pós-Graduação em Saúde Pública. Faculdade de Saúde Pública. Universidade de São Paulo. São Paulo, SP, Brasil

[II] Departamento de Epidemiologia. Faculdade de Saúde Pública. Universidade de São Paulo. São Paulo, SP, Brasil

Correspondence:
Raquel da Rocha Paiva Maia
Rua Roque Garcia, 363 Loteamento Santo Afonso
69908-836 Rio Branco, AC, Brasil
E-mail: raquelmaia@usp.br

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RESUMO

OBJETIVO: Analisar estudos que avaliaram o papel de infecções e de medidas indiretas de exposição às infecções no risco de leucemia infantil, principalmente da leucemia linfocítica aguda.

MÉTODOS: A busca nas bases de dados Medline, Lilacs e SciELO utilizando-se inicialmente os descritores "leucemia infantil" e "infecção" e, posteriormente, pesquisando-se as palavras "leucemia infantil" e "infecção ou doença materna" ou "aleitamento materno" ou "frequência à creche" ou "vacinação" recuperou 62 publicações que atenderam aos seguintes critérios de inclusão: amostra composta por sujeitos com idade inferior ou igual a 15 anos; análise específica de casos diagnosticados com leucemia linfocítica aguda ou todas as leucemias; avaliação de exposição materna ou infantil a infecções (ou medidas indiretas de exposição à infecção) e risco de leucemia.

RESULTADOS: Globalmente, os 23 estudos que avaliaram infecções nas crianças suportam a hipótese de que a ocorrência de infecções no início da infância reduz o risco de leucemia, mas existem discordâncias intra e entre estudos. A avaliação por meio das medidas indiretas de exposição à infecção mostrou evidências de redução do risco de leucemia associado principalmente com frequência à creche. Mais de 50,0% dos 16 estudos que avaliaram exposição materna à infecção observaram aumento do risco de leucemia associado com episódios de gripe, pneumonia, varicela, herpes zoster, infecção do trato genital inferior, doença de pele, doenças sexualmente transmissíveis, vírus Epstein-Barr (EBV) e *Helicobacter pylori*.

CONCLUSÕES: Embora nenhum agente infeccioso específico tenha sido identificado, as evidências científicas são sugestivas de que a exposição a infecções interfere na etiologia da leucemia infantil.

DESCRITORES: Crianças. Leucemia, etiologia. Causalidade. Infecção. Revisão.

INTRODUCTION

Leukemia makes up about one third of all malignancies in the 0-14 year old age group. The most common subtype, acute lymphoblastic leukemia (ALL), represents about 80.0% of these cases.[57] The incidence rate of ALL was estimated as 35.2 per million children aged under 15 in Brazil, and children under five are the most affected.[60]

Potential risk factors for childhood leukemia (CL) are conflicting. Exposure to ionizing radiation, commonly accepted as a cause of leukemia, does not explain all cases of leukemia in children.[5] The etiology of CL has a multifactorial character. Leukemic cells that carry genetic alterations arise mainly before birth. Translocation between chromosomes 12 and 21 causes fusion of the TEL and AML1 gene; producing aberrant proteins that inhibit gene activity and change the capacity for self-renewal and differentiation of hematopoietic stem cells; this change represents the most common structural genetic abnormality in children with leukemia.[45,74] About 1.0% of healthy newborns have this translocation and one leukemic clone generated in the uterus, however, they do not develop disease.[45] This fact and the low correlation between identical twin ALL (about 5,0% in infants 2-6 years) suggests that the disease probably begins in uterus, but a postnatal event is required for it to develop; this is known as a "two hit model".[16,17] Studies have tested whether infections may be involved in the etiology of CL. Three main hypothesis can explain the impact infections have on the disease development.

Smith[76] suggested that infection during pregnancy allows the infectious agent to be transmitted to the fetus and cause genetic instability, which leads to increased risk of developing c-ALL (B-cell precursor of common ALL) up to five years of age. This proposal would explain the peak occurrence of ALL in the 2-5 year old age group.

The hypothesis of "delayed infection", proposed by Greaves[17,19] suggests that the occurrence of common infections early in life may play a protective role against

Table 1. Review of studies on maternal infection and risk of childhood leukemia, 1973-2011.

Reference	Place	Study design	Infectious agent or disease	Disease	Risk (95%CI)
Increased risk					
Hakulinen et al[21] (1973)	Finland	BC	Asian influenza	CL	Exposed incidence: 68.1/million Unexposed incidence: 4.2/million; P = 0.048
Austin et al[2] (1975)	Los Angeles	BC	Influenza	CL	RR 3.4
Vianna & Polan[83] (1976)	USA	ECO	Chicken pox	CL	Expected incidence < 1 Observed incidence = 3
Till et al[78] (1979)	England	CC	Varicella and herpes zoster	ALL	Number cases higher than expected (2 of 54)
Mckinney et al[43] (1987)	IREESC	CC	Skin disease	CL	RR 2.3 (1.1;4.7)
Buckley et al[8] (1994)	USA Canada	CC	Any maternal infection	ALL	OR 1.5 (p < 0.05)
Naumburg et al[47] (2002)	Sweden	CC	Lower genital tract infection	ALL CL	OR 1.63 (1.04;2.53) OR 1.78 (1.17;2.72)
Lehtinen et al[35] (2003)	Finland Iceland	CC	*Epstein-Barr* virus	ALL	OR 2.9 (1.5;5,8)
Lehtinen et al[36] (2005)	Finland Iceland	CC	Helicobacter pylori	CL	OR 2.8 (1.1;6.9)
Kwan et al[33] (2007)	California	CC	Influenza/pneumonia	ALL CL	OR 1.89 (1.24;2.89) OR 1.74 (1.18;2.57)
			Sexually transmitted diseases	ALL CL	OR 4.85 (1.24;18.96) OR 6.33 (1.65;24.27)
Tedeschi et al[77] (2007)	Finland Iceland	CC	*Epstein-Barr* virus	ALL	OR 1.9 (1.2;3.0)
Non-significant effect or no association					
Randolph & Heath[59] (1974)	USA	BC	Influenza	CL	No consistent increased incidence
Curnen et al[12] (1974)	Connecticut	ECO	Influenza, chickenpox, whooping…	CL	No significant positive correlations
Dockerty et al[13] (1999)	New Zealand	CC	Influenza Cold sores/oral herpes	CL	OR 0.58 (0.24;1.41) OR 0.70 (0.25;1.99)
Mckinney et al[44] (1999)	Scotland	CC	Respiratory tract Genitourinary	ALL	OR 1.64 (0.60;4.46) OR 1.18 (0.50;2.79)
Infante-Rivard et al[24] (2000)	Quebec	CC	Recurrent infections	ALL	OR 1.09 (0.65;1.84)

BC: Birth cohort study; CC: Case-control study; ECO: Ecological study; CL: Childhood leukemia; ALL: Acute lymphoblastic leukemia; RR: Relative risk

ALL (especially subtype c-ALL). Whereas limited exposure to infection in this period of life increases the risk of disease by enhancing the possibility of abnormal immune response to infection acquired later.

The observation of temporary CL clusters in relatively isolated communities after increased entry of new individuals into these populations has provided support for the formulation of the "population mixing" hypothesis. Kinlen[27,28] suggests that the introduction of a specific infectious agent in a non-immune population could cause an abnormal immune response to infection by this pathogen and cause a transient increase in leukemia cases.

This article reviews studies related to Smith and Greaves' hypothesis on the role of infections and indirect measures of infection exposure on the risk of childhood leukemia, especially ALL.

METHODS

In order to identify eligible studies published before January 3, 2012, a search was made in three scientific publication databases: Medline,[a] Lilacs[b] and SciELO.[c] Studies with subjects age ≤ 15 years old and specific analysis of cases diagnosed as ALL and/or total leukemia were included in this review. The search considered possible associated factors: maternal or infant exposure to infections or proxy of infections (day care attendance, birth order, breastfeeding, vaccination).

The descriptors used for searching in the Medline database were: infection and childhood leukemia. The preliminary list included 612 publications. We pre-selected articles by reading titles and abstracts and created a second list of 145 potentially eligible studies. The inclusion criteria were met in 47 of those 145 articles. The same descriptors were used to search in the SciELO

[a] PubMed: the bibliographic database [Internet]. Bethesda (MD): National Library of Medicine (US). 1960s. Available from: http://www.ncbi.nlm.nih.gov/pubmed

[b] LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde [Internet]. São Paulo (BR): Bireme/OPS/OMS. 1982. Available from: http://lilacs.bvsalud.org/

[c] SciELO: Scientific Electronic Library Online [Internet]. São Paulo (BR): Bireme/OPS/FAPESP/CNPq. 1998. Available from: http://www.scielo.org/php/index.php?lang=en

and Lilacs databases. However, the term infection was replaced by infect$. The use of "$" symbol allows recording of words with the same root. The results included eight and fourteen studies, respectively. None met the inclusion criteria.

We looked for studies in the three databases using the descriptors "childhood leukemia", with the addition of words: infection or maternal disease, breastfeeding, day care, vaccination and birth order. We found a further 15 studies that met inclusion criteria and had not previously been screened.

RESULTS

This review included 62 studies: 85.5% were case-control, 9.7% cohort and 4.8% ecological studies. The studies were conducted in Europe, North America, Asia, Africa, and Oceania and published between 1973 and 2011.

Direct assessment of exposure to infection in the mothers and children

Maternal infection

The association between maternal infection during pregnancy and CL was evaluated in 16 studies, and statistically significant increased risks of leukemia were detected in 11[2,8,21,33,35,36,43,47,77,78,83] (Table 1). Associated infections were: influenza, pneumonia, chickenpox, herpes zoster, lower genital tract infection, skin disease, sexually transmitted diseases, Epstein-Barr virus (EBV), and *Helicobacter pylori*. Laboratory tests were performed for antibodies in maternal serum during pregnancy in three studies.[35,36,77] Maternal infection with EBV was associated with a significantly increased risk of ALL in two studies (odds ratio [OR] 2.9, 95% confidence interval [95%CI] 1.5;5.8; OR 1.9, 95%CI 1.2;3.0),[35,77] and Lehtinen et al[36] found a high risk of CL (but not ALL) associated with *Helicobacter pylori* infection. Naumburg et al[47] identified a significantly increased risk of both ALL (OR 1.63, 95%CI 1.04;2.53) and CL (OR 1.78, 95%CI 1.17;2.72) associated with lower genital tract infections. Likewise, Kwan et al[33] showed that the risk of ALL and CL was increased in children whose mothers had influenza/pneumonia and sexually transmitted diseases during the pregnancy. No statistically significant association was found between maternal infection and leukemia in five studies.[12,13,24,44,59]

Childhood infection

Table 2 shows twenty-three studies that evaluated the association between childhood infection and leukemia. Among those that analyzed infections in the first two years of life, five reported reduced risk of ALL associated with infection in the skin,[44] ears,[48,81] or gastrointestinal tract,[25] and episodes of roseola and/or fever and rash.[10] Other two studies detected a higher risk of ALL in children with more frequent episodes of upper respiratory tract infection,[9,64] fungal infection[64] and chickenpox.[9] A further five studies found reduced risk associated with some diseases and increased risk associated with others.[13,52,66,67,75] The association between common cold, fever, history of infection in the infant and leukemia was not significant in two studies.[47,82]

Exposure to infection at any time prior to diagnosis was examined in six studies.[25,38,40,43,68,70] A protective effect against leukemia in children with herpes labialis,[68] chickenpox,[70] and ear infection was detected.[38] Mckinney et al[43] and Jourdan-Da Silva et al,[25] respectively, identified an increased risk of leukemia correlating with total number of illness and rubella episodes. Macarthur et al[40] found a reduced risk of ALL in children with mumps or measles, but the results were not precise.

The occurrence of infection at leukemia diagnosis or in the year before diagnosis was evaluated in seven studies.[10,29,41,56,68,70,71] Among those, four performed laboratory tests to investigate exposure to specific infections. Petridou et al[56] found a lower risk of ALL associated with EBV, human herpes virus 6 (HHV6), and mycoplasma exposure, and increased risk associated with parainfluenza. Other two studies[41,71] identified increased risk of ALL in children exposed to the herpes simplex virus 1 and 2, hepatitis B virus, and EBV. Schlehofer et al[68] found no significant association between EBV infection, HHV6, parvovirus B19, or the adeno-associated virus and ALL.

Indirect assessment of exposure to infections in childhood

Daycare attendance

Table 3 presents information on studies that investigated the association between daycare attendance and leukemia. Nine studies identified a statistically significant reduced risk of leukemia related to daycare attendance.[15,24-26,37,38,52,54,81] Perrilat et al[52] and Gilham et al[15] detected a more pronounced protective effect for children having started daycare in early life (OR 0.5, 95%CI 0.3;1.0 for age ≤ 6 months; OR 0.56, 95%CI 0.37;0.83 for age < 3 months) than in those having started daycare at older ages, but the trend for age of starting daycare was not statistically significant. In Jourdan-Da Silva et al,[25] a statistically significant association was only observed when daycare started before 3 months old (OR 0.6, 95%CI 0.4;0.8) and the trend was also statistically significant (p trend < 0.05).

In other eight studies no statistically significant association or effects were reported.[1,10,48,55,63,65,67,70] Neglia et al[48] did not find association even when the daycare began before 6 months of age.

Table 2. Review of studies on childhood infection and risk of leukemia, 1973-2011.

Reference	Place	Study design	Infectious agent or disease	Disease	Risk (95%CI)
Infection in the first 2 years of life: protective effect					
Dockerty et al[13,a] (1999)	New Zealand	CC	Eye infection	ALL	OR 0.2 (0.1;0.7)
Mckinney et al[44] (1999)	Scotland	CC	Skin infection	ALL CL	OR 0.2 (0.05;0.87) OR 0.2 (0.05;0.87)
Neglia et al[48] (2000)	USA	CC	Ear infection	ALL	Ear infection episodes reduced the risk: p trend = 0.026
Chan et al[10,a] (2002)	Hong Kong	CC	Roseola and/or fever + rash	ALL	OR 0.33 (0.16;0.68)
Perrilat et al[52,a] (2002)	France	CC	Surgical procedures: ear, nose, throat	CL	OR 0.4 (0.2;0.9)
Jourdan-da Silva et al[25,a] (2004)	France	CC	≥4 gastrointestinal infections	ALL	OR 0.1 (0.03;0.6)
Rosembaum et al[66,a] (2005)	New York State	CC	Diarrhoea	ALL	OR 0.69 (0.48;0.99)
Simpson et al[75,a] (2007)	UK	CC	Eye infection	ALL	OR 0.7 (0.5;0.9)
Rudant et al[67,a] (2010)	France	CC	Otitis; Bronchiolitis/ other lower respiratory tract infections; Gastroenteritis	ALL	OR 0.7 (0.5;1.0) OR 0.3 (0.2;0.6) OR 0.3 (0.1;0.8)
Urayama et al[81] (2011)	California	CC	Ear infection: non-Hispanic children; Hispanic children	ALL	OR 0.39 (0.17;0.91) OR 0.48 (0.27;0.83)
Infection in the first 2 years of life: increased risk					
Dockerty et al[13,a] (1999)	New Zealand	CC	Influenza	CL ALL	OR 6.80 (1.81;25.66) OR 6.0 (1.4;26.2)
Perrilat et al[52,a] (2002)	France	CC	Mumps	CL	OR 3.2 (1.1;9.0)
Rosembaum et al[66,a] (2005)	New York State	CC	Otitis in the second year of life	ALL B lineage	OR 1.56 (1.02;2.37)
Roman et al[64] (2007)	UK	CC	Upper respiratory tract infection Fungal infection	ALL	OR 1.3 (1.0;1.7) OR 1.9 (1.1;3.2)
Simpson et al[75,a] (2007)	UK	CC	At least one infection	ALL	OR 1.6 (1.1;2.2)
Cardwell et al[9] (2008)	UK	CC	Upper respiratory tract infections; Chickenpox	ALL	OR 1.59 (1.02;2.49) OR 2.62 (1.12;6.13)
Rudant et al[67,a] (2010)	France	CC	Upper respiratory tract infections	ALL	OR 1.6 (1.3;2.0)
Infection in the first 2 years of life: non-significant effects or no association					
Van Steensel-Moll et al[82] (1986)	Netherlands	CC	Common colds; Fever	ALL	RR 0.8; p > 0.05; RR 0.9; p > 0.05
Naumburg et al[47] (2002)	Sweden	CC	History of infection in the postpartum	CL	OR 1.0 (0.50;2.04)
Infection at any time prior to the diagnosis: protective effect					
Schlehofer et al[68,a] (1996)	Germany	CC	Herpes labialis	CL	RR 0.38 (0.15;0.96)
Schuz et al[70,a] (1999)	Germany	CC	Chickenpox	AL	OR 0.8 (0.7;1.0)
Ma et al[38] 2(005)	California	CC	Ear infection (in non-Hispanic)	c-ALL	OR 0.32 (0.14;0.74)
Infection at any time prior to the diagnosis: increased risk					
Mckinney et al[43] (1987)	UK	CC	Number of illness episodes	CL	RR 1.9 (1.0;3.4)
Jourdan-da Silva et al[25,a] (2004)	France	CC	Rubella	ALL	OR 2.4 (1.4;4.1)
Infection at any time prior to the diagnosis: non-significant effect or no association					
Macarthur et al[40] (2008)	Canada	CC	Mumps Measles	ALL	OR 0.57 (0.13;2.52) OR 0.62 (0.25;1.27)
Infection at diagnosis or in the year before diagnosis: increased risk					
Schuz et al[70,a] (1999)	Germany	CC	Bronchitis Pneumonia	c-ALL	OR 1.9 (1.3;2.7) OR 2.6 (1.4;4.8)
Chan et al[10,a] (2002)	Hong Kong	CC	Tonsillitis	c-ALL	OR 2.96 (1.32;6.66)
Kroll et al[29] (2006)	Britain	ECO	Influenza	c-ALL	Influenza epidemic preceded peak of c-ALL

Continue

Continuation

Infection at diagnosis or in the year before diagnosis: laboratory analysis					
Schlehofer et al[68,a] (1996)	Germany	CC	Epstein-Barr Virus Parvovirus B-19 Adeno-associated virus type 2 Human herpes virus type 6.	CL	RR 2.05 (0.99;4.23) RR 0.48 (0.14;1.69) RR 0.66 (0.29;1.50) RR 1.11 (0.54;2.28)
Petridou et al[56] (2001)	Greece	CC	Epstein-Barr virus Human herpes virus type 6 Mycoplasma Parainfluenza1,2,3	ALL	OR 0.4 (0.2;0.8) OR 0.5 (0.3;0.9) OR 0.1 (0.0;0.7) OR 1.9 (1.1;3.2)
Mahjour et al[41] (2010)	Iran	CC	Herpes Simplex Viruses 1 and 2; Epstein-Barr Virus; hepatitis B Virus	ALL	The prevalence of antibodies against HBsAg ($p = 0.002$), HSV1 ($p < 0.0001$), VCA ($p = 0.021$) and EA ($p < 0.0001$) antigens of EBV were higher in ALL patients.
Sehgal et al[71] (2010)	India	CC	Epstein Barr Virus	ALL	Significant increase in EBV in ALL patients ($p < 0.05$)

CC: Case-control study; ECO: Ecological study; CL: Childhood leukemia; ALL: Acute lymphoblastic leukemia; AL: Acute leukemia; c-ALL: B-cell precursor common AL; RR: Relative risk; OR: Odds ratio; 95%CI: 95% confidence interval
[a] Study listed more than once in the table

Birth order

The relationship between birth order and leukemia was evaluated in 21 studies (Table 4). Van Steensel-Moll[82] detected increased ALL risk in children with lower birth order (first-born). Four studies found a protective effect associated with higher birth order.[14,56,67,81] Of these, Dockerty et al[14] observed ALL risk reduction with increased parity (p trend < 0.001) in a sample of 2,942 cases and the same number of controls in England and Wales.

Infante-Rivard et al[24] detected a reduced ALL risk in children aged four and over who had at least one older sibling in the first year of life (OR 0.46, 95%CI 0.22;0.97), but they observed a higher ALL risk in children under four years old who had at least one older sibling at diagnosis (OR 4.54, 95%CI 2.27;9.07).

Three studies found higher ALL risk related to higher birth order.[25,61,73] Shu et al[73] in the United States (1,842 cases of ALL, 1,986 controls) detected positive association (OR 2.0, 95%CI 1.3;3.0; p trend < 0.01). Abdul Rahman et al[1] identified reduced risk of acute leukemia related to lower birth order.

However, 11 studies showed no statistically significant association.[15,26,44,46,48,50,52,55,63,70,85] Westergaard et al,[85] in a cohort study in Denmark, found a reduced risk of ALL related to higher birth order, but the result was not precise (relative risk [RR] 0.72, 95%CI 0.46;1.13).

Assessment of child immune status

Breastfeeding

Table 5 lists the studies that investigated the association between leukemia and breastfeeding. A protective effect in children with more breastfeeding time was detected in five of those 17 studies.[13,24,53,67,72] Shu et al[72] identified a reducing ALL risk with increased breastfeeding time (p trend 0.003). Children who were breastfed for more than six months had a lower risk of ALL (OR 0.72, 95%CI 0.60;0.87) than those who were never breastfed. Two studies found a higher ALL risk in children breastfed for less than six months.[6,7]

Ten studies found no association between breastfeeding and CL.[10,25,32,34,40,46,55,70,79,84] In a large study (1,342 CL cases) conducted in the United Kingdom, no association was seen with breastfeeding duration (p trend 0.90).[34]

Vaccination

Eleven studies explored associations between vaccination and leukemia (data not shown).[3,8,13,20,39,40,42,43,49,55,70] Five of these identified a reduced risk in children who were vaccinated (any vaccine)[13,43] or who had been immunized with BCG[49] and Hib (*Haemophilus influenzae* type B)[20,39] vaccine. Ma et al[39] detected a lower risk of ALL (OR 0.81, 95%CI 0.66;0.98) and CL (OR 0.81, 95%CI 0.68;0.96) associated with the Hib vaccine. Furthermore, Schuz et al[70] observed an increased c-ALL risk in children who had received less than four vaccines compared to those who had received six or more.

On the other hand, Buckley et al[8] found an increased risk of c-ALL (OR 1.7, $p < 0.01$) in children who received the MMR (measles, mumps and rubella) vaccine. Four studies found no statistically significant association between these variables.[3,40,42,55]

Table 3. Review of studies on daycare attendance and risk of childhood leukemia, 1973-2011.

Reference	Place	Study design	Disease	Variables	Risk (95%CI)
Protective effect					
Petridou et al[54] (1993)	Attica (Greece)	CC	CL	Attendance at day-care for > 3 months in the first two years of life	OR 0.28 (0.09;0.88)
Infante-Rivard et al[24] (2000)	Quebec	CC	ALL	Entry at ≤ 2 years old	OR 0.49 (0.31;0.77)
Perrilat et al[52] (2002)	France	CC	AL	Age at start of day care ≤ 6 months *versus* no day-care	OR 0.5 (0.3;1.0)
Ma et al[37] (2002)	California	CC	ALL	Children who had more total child – hours of attendance at day-care	OR 0.64 (0.45;0.95)
Jourdan-Da Silva et al[25] (2004)	France	CC	ALL	Age at start of day-care < 3 months *versus* no day-care	OR 0.6 (0.4;0.8)
Ma et al[38] (2005)	California	CC	ALL	Children (non-Hispanic white) who had more time of attendance at day-care	OR 0.42 (0.18;0.99)
Gilham et al[15] (2005)	UK	CC	ALL	Formal day care in the first year of life Age at start of day-care < 3 months *versus* no day-care	OR 0.48 (0.37;0.62) OR 0.56 (0.37;0.83)
Kamper-Jorgensen et al[26] (2008)	Denmark	CC	ALL	Childcare in the first 2 years	OR 0.68 (0.48;0.95)
Urayama[81] (2011)	California	CC	ALL	Attendance day-care by age 6 months (non-Hispanic white)	OR 0.83 (0.73;0.94)
Non-significant effect or no association					
Roman et al[63] (1994)	England	CC	ALL	Child's attendance at preschool playgroup	OR 0.6 (0.2;1.8)
Petridou et al[55] (1997)	Greece	CC	CL	Day-care: Yes *versus* No	OR 0.83 (0.51;1.37)
Schuz et al[70] (1999)	Germany	CC	c-ALL	Deficit in social contact	OR 1.0 (0.8;1.2)
Neglia et al[48] (2000)	USA	CC	ALL	Age at start of day care < 6 months	OR 0.91 (0.72;1.15)
Rosenbaum et al[65] (2000)	New York State	CC	ALL	Duration of out-of-home care (months): stayed home (*versus* > 36)	OR 1.32 (0.70;2.52)
Chan et al[10] (2002)	Hong Kong	CC	c-ALL	Attendance at day-care during first year of life	OR 0.93 (0.63;1.36)
Abdul Rahman et al[1] (2008)	Malaysia	CC	AL	Attendance in day-care (Yes *versus* No)	OR 1.12 (0.65;1.92)
Rudant et al[67] (2010)	France	CC	ALL	Full-time day-care attendance in the first year of life	OR 0.8 (0.6;1.1)

CC: Case-control study; CL: Childhood leukemia; ALL: Acute lymphoblastic leukemia; AL: Acute leukemia; c-ALL: B-cell precursor common ALL; OR: Odds ratio; 95%CI: 95% confidence interval

DISCUSSION

Greaves[17,19] argues that infections play an important role in the natural history of ALL, and especially c-ALL, considering the two hit model involving two independent genetic mutations. The first event concerns the initial genetic damage which occurs in the uterus during B cell precursor expansion producing a pre-leukemic clone. The second concerns postnatal genetic mutation that can lead to disease development.

According to this review, more than 50.0% of studies investigating maternal exposure to infection observed increasing risk of CL. These results support the hypothesis proposed by Smith.[76] It is possible that exposure to *in utero* infection is one of the factors involved in genetic damage in the first "hit" referred to by Greaves.[17]

Results of childhood exposure to infections support the hypothesis that infection early in life (especially the first year of life) is associated with reduced risk of ALL. Even so, data are conflicting. Some factors may contribute to the apparent inconsistency between studies.[d] First, infections may only be involved in the etiology of a specific subtype of ALL (most probably c-ALL). For this reason, recent studies have analyzed all cases of ALL and specifically c-ALL. Another difficulty concerns when the infections occurred. Studies evaluating infection occurrence

[d] Edgar K, Morgan A. Does infections cause or prevent childhood leukemia? A review of the scientific evidence. London: Children with Leukemia; 2008 [cited 2013 Oct 31]. Available from: http://www.childrenwithcancer.org.uk/infection-and-leukaemia

Table 4. Review of studies on birth order and risk of childhood leukemia, 1973-2011.

Reference	Place	Study design	Disease	Variables	Risk (95%CI)
Negative association: protective effect associated with higher birth order/ increased risk associated with lower birth order					
Van steensel-moll[82] (1986)	Netherlands	CC	ALL	There were more first-born children in cases	RR 1.8 (1.1;2.7)
Infante-Rivard et al[24,a] (2000)	Quebec	CC	ALL	Having older siblings in the 1st year of life (in cases diagnosed at 4 years of age or later)	OR 0.46 (0.22;0.97)
Petridou et al[56] (2001)	Greece	CC	ALL	Birth order: other *versus* first	OR 0.5 (0.3;0.9)
Dockerty et al[14] (2001)	England Wales	CC	ALL	Parity ≥ 5	OR 0.52 (0.34;0.80)
Rudant et al[67] (2010)	France	CC	ALL	Parity ≥ 4 *versus* 1	OR 0.5 (0.3;0.8)
Urayama[81] (2011)	California	CC	ALL	Birth order ≥ 4 *versus* 1(in children non-Hispanic white)	OR 0.44 (0.21;0.92)
Positive association: increased risk associated with higher birth order/ protective effect associated with lower birth order					
Infante-Rivard et al[24,a] (2000)	Quebec	CC	ALL	Having older siblings at time of diagnosis (in children diagnosed before 4 years of age)	OR 4.54 (2.27;9.07)
Shu et al[73] (2002)	USA	CC	ALL	Birth order ≥ 4 *versus* 1	OR 2.0 (1.3;3.0)
Reynolds et al[61] (2002)	California	CC	ALL	Number of previous live births ≥ 3 *versus* 0 (in children aged < 2 years)	OR 1.53 (1.00;2.34)
Jourdan-Da Silva et al[25] (2004)	France	CC	ALL	Birth order ≥ 4 *versus* 1	OR 2.0 (1.1;3.7)
Abdul Rahman et al[1] (2008)	Malaysia	CC	AL	Number of elder siblings < 2 *versus* ≥ 2	OR 0.37 (0.22;0.64)
Non-significant effect or no association					
Roman et al[63] (1994)	England	CC	ALL	Number of siblings ≥ 2 *versus* 0	OR 0.8 (0.2;3.0)
Westergaard et al[85] (1997)	Denmark	COH	ALL	Birth order ≥ 4 *versus* 1	RR 0.72 (0.46;1.13)
Petridou et al[55] (1997)	Greece	CC	CL	Risk decreases with increasing birth order	OR 0.74 (0.48;1.15)
Schuz et al[70] (1999)	German	CC	c-ALL	First-born child (yes *versus* no)	OR 1.1 (1.0;1.4)
Mckinney et al[44] (1999)	Scotland	CC	ALL CL	Parity (0 *versus* 1 or more)	OR 0.81 (0.52;1.25) OR 0.82 (0.55;1.23)
Neglia et al[48] (2000)	USA	CC	ALL	Number of older siblings ≥ 2 *versus* 0	OR 1.05 (0.88;1.26)
Perrilat et al[52] (2002)	France	CC	ALL	Birth order ≥ 4 *versus* 1	OR 1.4 (0.7;2.8)
Murray et al[46] (2002)	Ireland	COH	ALL	First-born *versus* Not first born	RR 0.98 (0.71;1.36)
Okcu et al[50] (2002)	Texas	CC	ALL CL	Parity ≥ 5 *versus* 0	OR 1.0 (0.1;7.8) OR 0.5 (0.1;4.3)
Gilham et al[15] (2005)	UK	CC	ALL	Number of siblings ≥ 3 *versus* none	OR 0.99 (0.74;1.30)
Kamper-Jorgensen et al[26] (2008)	Denmark	CC	ALL	Older siblings > 2 *versus* 0	RR 0.93 (0.72; 1.19)

CC: Case-control study; COH: Cohort study; CL: Childhood leukemia; ALL: Acute lymphoblastic leukemia; AL: Acute leukemia; c-ALL: B-cell precursor common ALL; RR: Relative risk; OR: Odds ratio; 95%CI: 95% confidence interval

[a] Study listed more than once in the table

at any time prior to diagnosis showed more inconsistent results. Future studies should evaluate the infection occurrence in specific periods such as the first year and one year before diagnosis. In this way, data would help assess whether a lack of immune system modulation in early childhood, associated with a delay in infection occurrence, increases the risk of ALL. In relation to the display window, infections detected near the leukemia diagnosis may be due to an increased susceptibility to infections resulting from the effects of leukemia itself. Some protocols exclude data on infections occurring in the three months before diagnosis date to avoid bias.

Table 5. Review of studies on breastfeeding and risk of childhood leukemia, 1973-2011.

Reference	Place or group	Study design	Disease	Time of breast feeding	Risk (95%CI)
Negative association: protective effect associated with longer breastfeeding period/increased risk associated with shorter breastfeeding period					
Dockerty et al[13] (1999)	New Zealand	CC	ALL	> 1 year	OR 0.5 (p = 0.04)
Shu et al[72] (1999)	USA, Canada, Australia	CC	ALL	> 6 *versus* 0 More time breastfeeding	OR 0.72 (0.60;0.87) p trend = 0.0034
Infante-Rivard et al[24] (2000)	Quebec	CC	ALL	>3 months *versus* 0	OR 0.67 (0.47;0.94)
Bener et al[6] (2001)	United Arab Emirates	CC	ALL	0-6 months *versus* > 6	OR 2.47 (1.17;5.25)
Perrilat et al[53] (2002)	France	CC	AL	≥ 6 months *versus* 0	OR 0.5 (0.2;0.9)
Bener et al[7] (2008)	Qatar	CC	ALL	0-6 months *versus* > 6	Males: OR 3.1 (1.4;6.8) Females: OR 2.2 (0.8;6.32)
Rudant et al[67] (2010)	France	CC	ALL	≥ 6 months *versus* > 0	OR 0.7 (0.5;1.0)
Non-significant effect or no association					
Petridou et al[55] (1997)	Greece	CC	CL	yes *versus* no	OR 0.85 (0.52;1.41)
Schuz et al[70] (1999)	Germany	CC	c-ALL	2-6 months *versus* > 6	OR 1.2 (0.9;1.6)
UKCCS[79] (2001)	UK	CC	ALL	≥ 7 months *versus* 0	OR 0.89 (0.75;1.05)
Murray et al[46] (2002)	Ireland	COH	ALL	no *versus* yes	RR 0.98 (0.68;1.42)
Chan et al[10] (2002)	Hong Kong	CC	c-ALL	≥ 6 months (yes *versus* no)	OR 0.21 (0.03;1.76)
Lancashire & Sorahan[34] (2003)	UK	CC	ALL CL	ever *versus* never	OR 1.04 (0.86;1.26) OR 1.05 (0.89 ;1.23)
Jourdan-Da Silva et al[25] (2004)	France	CC	ALL	yes *versus* no	OR 1.1 (0.9;1.5)
Kwan et al[32] (2005)	California	CC	ALL	ever *versus* never	OR 0.99 (0.64;1.55)
Macarthur et al[40] (2008)	Canada	CC	ALL CL	7-12 months (yes *versus* no)	OR 1.02 (0.68;1.53) OR 1.00 (0.67;1.50)
Waly et al[84] (2011)	Oman	CC	ALL	No statistically significant difference	$\chi 2 = 3.816$, P = 0.282

CC: Case-control study; COH: Cohort study; CL: Childhood leukemia; ALL: Acute lymphoblastic leukemia; AL: Acute leukemia; c-ALL: B-cell precursor common ALL; RR: Risk relative; OR: Odds ratio; 95%CI: 95% confidence interval

The instrument used to directly assess exposure to infection is another limitation we found. Most studies used data from mothers via questionnaires for the recall of infection occurrence. This method is subject to misclassification bias, with differential recall between cases and controls. Only three of the studies in this review obtained clinical records to evaluate children's exposure to infection.[9,64,75] Although this latter method is not affected by recall bias, it does present other difficulties. The lack of a clinical records system with extensive population coverage and good quality data hinders the use of this instrument. Furthermore, the number of infections can be underestimated because the occurrence of common infections does not always mean that the mother seeks health service help. Simpson et al[75] compared results from clinical diagnoses of infection with those based on maternal self-report. They observed that mothers of cases and controls under-reported the frequency of infections in the first year of life. However, the degree of under-reporting appeared greater for mothers of cases than of controls.

Chang et al[11] used records of medically diagnosed infections and they found higher risk of ALL in children who had had acute respiratory infections and any infections before 1 year of age. The authors suggest that children who develop leukemia may have dysregulated immune function since early childhood strongly reacting to infections.

However, they do not refute the "delayed infection hypothesis" supported by several studies using proxy measures and state that their results are not relevant to asymptomatic infections or infections not requiring medical attention.

The difficulty in measuring the occurrence of infectious diseases in childhood leads epidemiologists to use proxy measures of exposure to infection: indirect measures that indicate levels of physical and social contact. These variables are easier to obtain, are less prone to recall bias, and probably include children with asymptomatic infections.

Daycare attendance has been widely used as an indicator of a child's level of social contact and therefore opportunity of contact with infectious agents. Interaction between children, parents, and staff, and the sharing of toys are factors that may contribute to increased transmission of infectious agents. Exposure to respiratory and gastrointestinal tracts infections are known to be more frequent in this type of environment.[23,51] In general, the studies in our review show

evidence supporting a reduced risk of ALL associated with daycare attendance, providing support to the hypothesis proposed by Greaves. In a meta-analysis, Urayama et al[80] found a reduced risk of ALL in two subgroups of children – those who attended day-care before two years of age and those where age at day-care attendance was not specified (any age before diagnosis).

Birth order has also been used as a proxy variable for infection since children with older siblings are more likely to be exposed to infection due to contact with their siblings.[d] Most studies showed no evidence of an association between these variables. Parity is probably influenced by selection bias. Couples with higher socioeconomic status (SES) tend to have fewer children so there may be some confounding effect if SES is assessed differently between groups (cases and controls). Moreover, Edgar & Morgan[d] report that studies generally do not differentiate between the firstborn and the only child. Then, the association of ALL with a history of abortion and reproductive failures may be a confounding factor.

The association between SES and CL has been discussed in the literature. SES does influence the level of exposure and vulnerability of individuals to certain diseases. However, some studies have shown that increased risk of CL seems to be associated with increased SES.[30,62] In Sao Paulo, Southwestern Brazil, Ribeiro et al[62] found a lower risk of leukemia in children living in areas with lower SES and in areas where a high percentage of families had more than seven members. However, in the review conducted by Poole et al,[58] the association direction seems to vary according to study design, place and time; they also highlighted comparison difficulties between studies because of differences in assessing SES. Measures such as family income and parental education presented an inverse association. Evaluation considering professional class revealed increased CL risk associated with higher SES in both ecological and individual approach studies.

Breast milk protects the child against infections and boosts the immune system contributing to its modulation.[22] It is therefore reasonable to assume that breastfeeding exerts a similar effect to early infection on a child's immunity inducing a protective effect against leukemia.[d] Most of the studies in our review did not identify a statistically significant association between ALL and breastfeeding duration. However, in a meta-analysis including 14 studies, Kwan et al[31] identified a protective effect from breastfeeding on ALL.

While not an actual infection, vaccine acts on the immune system as an infection does.[d] Results from the reviewed studies have provided some evidence of a protective effect from vaccination on the risk of ALL, especially regarding the Hib vaccine. One major difficulty with this variable is that high vaccination coverage makes it difficult to gauge the effect on CL.[d]

Although no specific etiological agent has been identified, results of the studies reviewed provide evidence that the lack of exposure to infections during early childhood, and consequent failure in modulation of the immune system, may increase the risk of developing leukemia by the occurrence of an abnormal immune response after exposure to a later infection, as reported by Greaves.[17,18] However, the mechanisms involved in this process are still not completely clear.

Schmiegelow et al[69] proposed in 2008 an explanation for the observed association between infections in early childhood and reduced risk of ALL: the adrenal hypothesis. This postulates that children with lower SES, thus subject to getting infections more often, have a lower risk of ALL, because changes in the hypothalamic-pituitary-adrenal axis induced by infection lead to increased cortisol plasma levels similar to those observed during antileukemic therapy, leading to pre-leukemic cell apoptosis. Furthermore, the immune system can adapt to high infectious loads preventing a more reactive inflammatory response induced by Th1 cytokines in that cortisol favors the production of anti-inflammatory Th2 cytokines. Azevedo-Silva et al[4] show differences in ALL incidence rates across Brazilian regions. Salvador and Aracaju, cities in the Northeast, had the lowest rates, while Curitiba, Southeast, and Goiania, Midwest, had the highest. Brazilian regions show very distinct social and economic profiles. These authors suggest that the differences in incidence rates could be due to an early exposure to infectious agents in children living in areas with characteristics favoring the continued exposure to such agents. The lower ALL incidence rates in children from those cities (less developed) would then support the adrenal hypothesis.

Besides the lack of immune system modulation, WIEMELS[86] reports another phenomenon that would leads to an increased risk of CL: children with dysregulated immune function at birth are at higher risk for developing leukemia due to constitutively lower expression of IL-10, a cytokine that is critical in preventing an overactive inflammatory response to pathogenic infections. This factor would explain why in some studies[11] children with ALL had significantly more clinically diagnosed infectious episodes in the first year of life compared to controls.

The purpose of this study was to review epidemiological studies related to two hypotheses which propose a role for infections in CL etiology. Considering the "two hit" model by Greaves,[17] it is possible that the Smith hypothesis may play a role in the first hit and delayed infection in the second. Overall, this review provides evidence supporting the role of infections in the natural history of CL. This justifies further research even though no specific infectious agent has so far been associated with

the disease. With regard to assessing exposure to infection or modulation of the immune system using a proxy, results were more consistent using daycare attendance than birth order, breastfeeding, or vaccination. Future studies should consider carefully evaluating exposure to infection at different stages of childhood. Accurate data on exposure period (in early childhood or near diagnosis), especially in relation to daycare attendance and the occurrence of infection episodes, are essential in eliminating potential bias and improving study accuracy. Furthermore, different subtypes of the disease require specific analysis because infectious agents can have distinct roles in the etiology of each subtype. Specific attention to these points, in addition to the contribution from genetic studies, is essential to help clarify the relationship between infections and CL etiology.

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