Published in final edited form as:
Blood Cells Mol Dis. 2009 ; 42(2): 117–120. doi:10.1016/j.bcmd.2008.10.006.

Infection and Pediatric Acute Lymphoblastic Leukemia

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Abstract

In this review, we provide an overview of recent findings from the Northern California Childhood Leukemia Study (NCCLS) on factors related to the immune system including child's vaccination history and measures of child's exposure to infectious agents, namely daycare attendance, infection during infancy, and parental social contact in the work place. We also provide suggestions for the next stages of studies.

Multiple lines of evidence support a role for infections in the etiology of childhood acute lymphoblastic leukemia (ALL), and there are two prominent hypotheses concerning the underlying mechanisms. Greaves hypothesized that delayed exposure to common infections leads to an increased risk of childhood leukemia, especially common pre-B ALL (cALL), which has a peak incidence in 2-5 year olds [1,2]. Greaves proposed that a minimum of two separate genetic events may be responsible for the development of cALL. The first event occurs spontaneously *in utero* during the expansion of B-cell precursors to establish a preleukemic clone; the second event occurs in the same mutated preleukemic clone following antigenic challenge early in life. Children who have a delayed exposure to common infectious agents develop a less well modulated immune system and may experience greater cell proliferation following common infections, and therefore, have an increased risk of the second mutation leading to the development of ALL [1,2]. A related hypothesis by Kinlen suggests that childhood leukemia might result from a rare response to a common but unidentified infection and that increased risks would occur when populations were mixed so that infected and susceptible individuals had an increased level of contact [3]. He later hypothesized that childhood leukemia is caused by a viral infection(s), the transmission of which is promoted by population mixing [4]. Both of these hypotheses are consistent with the proposition that leukemia may be caused by abnormal immune response to infections. The Greaves hypothesis emphasizes the importance of timing of exposure and does not focus on specific agents, while the Kinlen hypothesis appears to favor specific agents (although not yet identified).

Directly testing the hypotheses is challenging, because exposure and response to infections is difficult to quantify and no leukemogenic agent has been discovered so far. Specific agents have been assessed in ALL cells using open-ended laboratory methodology and leukemia samples, but no specific viral sequences were discovered among leukemia cases (MacKenzie

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2006). History of infections using serological methods has also been assessed, but as summarized by Ross *et al*, such studies of leukemia patients are mostly cross-sectional and unable to establish the temporal relationship between infection and leukemia incidence [5]. Timing is critical, as early infections are likely to positively modulate the immune system thereby reducing risk of leukemia, whereas later infections in children whose immune system was less well modulated may increase such risk [6]. Assessing timing via serology has been attempted with some circumstantial evidence supporting the Greaves hypothesis [7]; however samples taken after diagnosis may be affected by the disease, and will reflect infections at variable times in the past. Trying to assess history of infection through interview can also be problematic due to potential recall bias and misclassification of children who had asymptomatic infections [5]. Obtaining history of infection from medical records reduces the potential for recall bias, but it still does not capture asymptomatic infections. In addition, it is not uncommon for parents to care for children with minor infections without seeking help from medical professionals; relying solely on medical records will undoubtedly result in misclassification. Under these circumstances, using surrogate measures or markers of infection can be a good alternative in etiologic studies of childhood ALL.

Findings from the Northern California Childhood leukemia Study

Study Design

The NCCLS is an ongoing study which commenced in 1995. The study area includes 35 counties in Northern and Central California. In the NCCLS, incident cases of newly diagnosed childhood leukemia (age 0-14 years) are rapidly ascertained from major pediatric clinical centers in the study area, usually within 72 hours after diagnosis. Although case ascertainment is hospital-based, a comparison with all population-based cases recorded by the statewide California Cancer Registry (2000) confirms that the NCCLS protocol successfully identified 95 percent of all age-eligible newly diagnosed childhood leukemia cases among residents of the 5-county San Francisco metropolitan area and 76 percent of such cases in the other 30 counties. Medical records of all cases are abstracted and reviewed expeditiously by an expert hematologist to confirm diagnosis and subtype classification. Controls are randomly selected from the statewide birth certificate files maintained by the Center for Health Statistics in the California Department of Public Health and individually matched to cases on date of birth, sex, mother's race (white, African-American, or other), and Hispanic status (a child is considered Hispanic if either parent is Hispanic). Due to the unique demographic composition of the study area, approximately 42% of the cases enrolled in the NCCLS are Hispanic. The control to case ratio was 1:1 for cases diagnosed before December 1999 and 2:1 for those diagnosed afterwards. A detailed protocol for control selection has been reported elsewhere [8]. A personal interview with the primary care taker of each case or control subject, usually the biological mother, was scheduled as soon as consent was obtained. In addition, written immunization records were obtained directly from the parents or primary care providers for each subject.

Approximately 1,000 cases and 1,300 controls are expected to be enrolled by March 2009, making the NCCLS one of the largest case-control studies of childhood leukemia to date. Evaluating the role of immunologic factors is one of the main aims of the study, which has published a number of findings related to daycare attendance, infection during infancy, vaccination, and paternal social contact in the work place.

Daycare Attendance

The incidence of childhood leukemia, especially common ALL, is markedly higher in developed countries than in developing countries [9]. In developed countries, most exposure to common childhood infections results from contact with other children, and daycare attendance has been utilized as an indirect measure of early exposure to infectious agents [10]. Epidemiologic

studies have measured daycare attendance in different ways, such as binary characterization of attendance (i.e. ever vs. never), age first started daycare, and total duration of daycare attendance. In the NCCLS, we not only evaluated individual variables that reflect different aspects of daycare attendance, but also came up with a summary measure termed "child-hours of exposure", which effectively captured the variance contributed by individual daycare variables [11]. In our analysis of the NCCLS data, daycare attendance measured by child-hours was associated with a significantly reduced risk of ALL among non-Hispanic white children. Compared with children who did not attend any daycare, the odds ratio (OR) for those who had more than five thousand child-hours during infancy was 0.42 [95% confidence interval (CI) 0.18-0.99] for ALL and 0.33 for c-ALL (95% CI: 0.11-1.01), reflecting reduced risks of 58% and 67%, respectively. Tests for trend were also significant, thus supporting a dose-response relationship. The magnitude of effect associated with the same number of child-hours was stronger for daycare attendance during infancy than for daycare attendance anytime between birth and diagnosis, suggesting that exposure to infectious agents during infancy offers more protection than later exposure [12]. Intriguingly, daycare attendance was not associated with the risk of leukemia or ALL among Hispanic children. Compared with non-Hispanic white children included in the NCCLS, Hispanic children in the study were of higher birth order, lived with more other children before first grade, and were less likely to start daycare before age one. Therefore, contact with other children in a daycare setting might not have been an important source of exposure to infectious agents for the Hispanic children included in this study.

Given that a number of other studies have also addressed the relationship between daycare attendance and childhood ALL, we recently conducted a meta-analysis to appraise the overall evidence to date. The 14 relevant studies that we identified [6,12-24] generated a statistically significant summary odds ratio of 0.77 (95% CI 0.66-0.88) for daycare attended either before age one or two, or between birth to diagnosis (measured as ever/never in most studies) with a total of greater than 6000 leukemia cases, most of which were ALL (unpublished finding, manuscript under preparation). Summary results for nine studies of daycare attendance specifically before the age of one or two years showed a similarly reduced risk. Taken together, the current body of literature suggests that exposure to infectious agents early in life through daycare attendance or other social contacts is significantly protective against childhood ALL.

Infection during Infancy

In the NCCLS, respondents were asked specifically whether the index child experienced any severe diarrhea/vomiting, ear infection, persistent cough, mouth infection, eye infection, and influenza during infancy, and if yes, when the infection occurred, how long it lasted, whether it required contacting a doctor and obtaining a prescription. Our recent analysis showed that self-reported ear infection during infancy was associated with a significantly reduced risk of c-ALL (OR = 0.32, 95% CI: 0.14-0.74) in non-Hispanic white children [12].

A few other studies have also evaluated the possible role of infections during infancy in the etiology of ALL, with some showing a protective effect [16,25] and others suggesting the opposite [26]. As discussed earlier, it seems straightforward to directly obtain history of infections through interview and/or medical record abstraction. In reality, however, such a practice faces a number of methodological challenges. Paradoxically, surrogate measures or indicators of the potential of infections such as daycare attendance may be a good or even better measure to use in epidemiologic studies to evaluate the etiology of childhood ALL.

Vaccination

In the NCCLS, we made special effort to obtain histories of childhood vaccinations exclusively through written immunization records kept by the parents and/or primary care physicians,

which was a major improvement over many previous studies that relied on parental recall for exposure assessment. In addition to recording whether a subject had or had not received a specific vaccination, we collected data regarding number of doses, as well as date of each vaccination. These detailed data were useful for a more accurate and informative analysis. The NCCLS data showed that vaccinations against diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella were not associated with the risk of childhood ALL. On the other hand, *Haemophilus influenzae* type b (Hib) vaccination was associated with a significantly reduced risk of childhood ALL. The OR associated with each dose of Hib vaccine was 0.81 (95% CI: 0.66 - 0.98) [27].

Studies evaluating the relationship between vaccination and childhood leukemia were summarized in 2005 [27]. By that time, nine studies had reported a protective effect of certain types of vaccination, two studies had suggested the opposite, and three studies had found no association [27]. Additional studies have been published more recently and reported no association [28,29]. Vaccination practice in a given country is highly influenced by policies and recommendations made by health authorities that are usually affiliated with the government. If adherence to those recommendations is good, one would expect very little, if any, variation in vaccination coverage among individuals in the general population. As a result, investigators would be less likely to observe any association between vaccination and childhood leukemia, even if such an association truly exists. The timing of the NCCLS coincides with the window of opportunity to study the potential etiologic role of Hib vaccination. In the US, Hib vaccine has been administered on a large scale for more than 15 years. Future studies in the US may have difficulty assessing the role of Hib vaccine in the etiology of childhood ALL since most children will have received this vaccine following the recommended vaccination schedule at that time.

Parental Social Contact in the Work Place

Parental social contact in the work place is another proxy measure for a child's risk of infection that has been used to study the infectious etiology of childhood leukemia. Seven published studies other than NCCLS have examined parental social contact at work and childhood leukemia risk, and have produced inconsistent results [22,30-35]. Four of the seven studies found a positive association between higher parental occupational social contact and childhood leukemia risk especially for children living in the rural areas [30-33], while three other studies found no association. Several factors may have contributed to the inconsistencies [22,34,35]. Most of the studies did not assess the role of maternal social contact at work since the information on maternal occupation was not routinely available in those studies [30-35]. In addition, all of the studies had information on father's employment at only one or two points in time: at birth [22,30-33,35], at the time of child's death [34], or at the time of diagnosis [22,35]; none of the studies included information on the duration of the job. It may be important to account for the duration of the parental occupation since a parent's probability of being in contact with carriers of infectious agents may rise with increasing duration of the work.

In the NCCLS, parents were interviewed about history of employment after child's birth up to the age of three, including the duration of each job held. An index of occupational social contact months was created using the level of social contact assigned to each job and the duration of the occupation. The results showed that increasing levels of parental social contact in the work place is associated with an increased risk of childhood ALL only for children living in rural areas when the duration of the occupation was considered; no significant associations were observed when duration of the parental occupation was ignored [36].

The NCCLS results suggest that duration of parental occupation may be an important variable to include when evaluating the association between parental social contact at work and childhood leukemia. Since NCCLS is the first study to include duration of parental occupation

and the number of subjects living in the rural areas is small, the results need to be replicated by future studies.

Looking into the Future

To date, numerous epidemiologic studies have provided consistent yet indirect support for the role of infections in the etiology of childhood ALL. What else can be done to advance our understanding of this important topic?

Trying to identify specific agents is certainly one possible direction. The utility of cross-sectional serologic studies within case-control studies is questionable, since it is difficult to establish temporal relationship between infection and leukemia incidence. Analyzing specimens collected at birth (e.g. cord blood or Guthrie cards routinely collected for purpose of genetic screening), maternal blood specimens obtained during pregnancy, or pediatric pre-diagnostic specimens could be more informative. Given the rarity of childhood leukemia, it is not feasible to establish a cohort or "biological sample bank" for the study of this disease. However, efforts are under way to utilize existing large cohort studies to explore some aspects of leukemogenesis. A group of large cohorts comprising over one million subjects will be followed for leukemia incidence in coming years, under the direction of the International Childhood Cancer Cohort Consortium (I4C) [37]. Given that the initial genetic changes that lead to ALL are much more frequent than the disease diagnosis, these cohort studies may be able to examine what pattern of infections are protective among children born with mutations that are linked to leukemia. For example, 1 in 100 children are born with a leukemia-associated chromosomal translocation, *TEL-AML1* [38], a genetic change known to occur *in utero* in children who develop leukemia [39]. Only approximately 1 in 8000 children will eventually develop leukemia with this mutation. Understanding the pattern of immune modulation, particularly infections and vaccinations among those *TEL-AML1* carriers who remain healthy, will provide important insight into the modulating role of infections and may help us develop preventive interventions. Maternal and child samples collected in such cohorts can be used to screen for patterns of infections, as well as children's response to infections. Technologic advances in the last few years have made it possible to assess a large number of parameters, such as cytokine profiles and specific antibodies, using microarrays. Additional resources such as neonatal blood spots and maternal pregnancy blood specimens, both of which are banked for all children born in California, may also be appropriate for this research.

An intriguing possibility was suggested by a recent report demonstrating a high prevalence of adenovirus C infection among newborns who later developed leukemia compared to newborns who did not develop leukemia [40]. If confirmed, this result is suggestive of a "hit and run" mechanism, as adenovirus C is not present in pediatric leukemias [41]. The mechanism by which adenovirus would impact leukemogenesis would likely not be related to the immune modulation (infections early in life) or immune-stimulatory (infections immediately preceding diagnosis) arguments made above. An infection *in utero* during a period of immunologic naivety would not modulate the immune system but could elicit anti-viral cellular mechanisms including viral and somatic gene methylation.

Nevertheless, it is important to note that there may not be a specific agent or agents that "cause" leukemia. Search for specific viruses as transforming agents in leukemia cells has yielded negative results; and common infections are more promising candidates, with the pattern of infections more critical than their specific identities. Epidemiologic studies have helped pinpoint the potential role of infection and will continue to help us decipher the etiology of childhood ALL, as long as we strive to sharpen our tools. First, improving exposure assessment is critical to enhancing the precision of epidemiologic studies. Both direct and proxy measures of infections need to be assessed in a more focused and detailed way. This includes an exposure

assessment strategy that accounts for the various sources of a child's potential exposure to infectious agents, both in and outside the home. Second, it will be important to classify the disease more precisely. Different subtypes may be etiologically distinct with regard to the role of infectious agents. Third, additional support for an immune-related etiology of childhood ALL and specific clues about biological mechanisms can be obtained by examining the role of genetic susceptibility conferred by variation in immune-regulatory genes, such as those residing in the major histocompatibility complex. Finally, given the rarity of childhood ALL, the imprecise results generated by many previous studies, and the need to further categorize the disease, it will be very helpful to have similar protocols across individual studies and conduct pooled analyses in the context of the recently assembled International Childhood Leukemia Consortium (CLIC), a group of 14 epidemiologic studies of childhood leukemia representing populations from 10 different countries, and within the I4C cohort consortium mentioned above.

Acknowledgments

This paper is based on a presentation at a Focused Workshop on “Immunity and Infection in the Etiology of Leukemia: a Workshop” sponsored by The Leukemia & Lymphoma Society and held in Sausalito, CA, Nov. 14-16, 2007.

References

1. Greaves MF. Speculations on the Cause of Childhood Acute Lymphoblastic Leukemia. Leukemia 1988;2:120–125. [PubMed: 3278171]
2. Alexander F, Chan L, Lam T, et al. Clustering of Childhood Leukaemia in Hong Kong: Association with the Childhood Peak and Common Acute Lymphoblastic Leukaemia and with Population Mixing. British Journal of Cancer 1997;75:457–463. [PubMed: 9020498]
3. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet 1988;2:1323–1327. see comments. [PubMed: 2904050]
4. Kinlen LJ. Infection and childhood leukemia. Cancer Causes and Control 1998;9:237–239. editorial; comment. [PubMed: 9684703]
5. Ross, JA.; Spector, LG. Cancers in children. In: Schottenfeld, D.; Fraumeni, JF., editors. Cancer epidemiology and prevention. 3rd. Oxford; New York: Oxford University Press; 2006. p. xviiip. 1392
6. Chan LC, Lam TH, Li CK, et al. Is the timing of exposure to infection a major determinant of acute lymphoblastic leukaemia in Hong Kong? Paediatr Perinat Epidemiol 2002;16:154–165. [PubMed: 12060313]
7. Petridou E, Dalamaga M, Mentis A, et al. Evidence on the infectious etiology of childhood leukemia: the role of low herd immunity (Greece). Cancer Causes Control 2001;12:645–652. [PubMed: 11552712]
8. Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004;159:915–921. [PubMed: 15128601]
9. Greaves MF, Colman SM, Beard ME, et al. Geographical distribution of acute lymphoblastic leukaemia subtypes: second report of the collaborative group study. Leukemia 1993;7:27–34. [PubMed: 8418376]
10. Alexander FE, McKinney PM, Cartwright RA. Migration patterns of children with leukaemia and non-Hodgkin's lymphoma in three areas of northern England. Journal of Public Health Medicine 1993;15:9–15. [PubMed: 8471307]
11. Ma X, Buffler PA, Selvin S, et al. Daycare attendance and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2002;86:1419–1424. [PubMed: 11986774]
12. Ma X, Buffler PA, Wiemels JL, et al. Ethnic difference in daycare attendance, early infections, and risk of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev 2005;14:1928–1934. [PubMed: 16103439]

13. Dockerty JD, Skegg DC, Elwood JM, Herbison GP, Becroft DM, Lewis ME. Infections, vaccinations, and the risk of childhood leukaemia. British Journal of Cancer 1999;80:1483–1489. [PubMed: 10424755]
14. Gilham C, Peto J, Simpson J, et al. Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. Bmj 2005;330:1294. [PubMed: 15849205]
15. Infante-Rivard C, Fortier I, Olson E. Markers of infection, breast-feeding and childhood acute lymphoblastic leukaemia. British Journal of Cancer 2000;83:1559–1564. [PubMed: 11076669]
16. Jourdan-Da Silva N, Perel Y, Mechinaud F, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. Br J Cancer 2004;90:139–145. [PubMed: 14710221]
17. Kamper-Jorgensen M, Woodward A, Wohlfahrt J, et al. Childcare in the first 2 years of life reduces the risk of childhood acute lymphoblastic leukemia. Leukemia 2008;22:189–193. [PubMed: 17690702]
18. Neglia JP, Linet MS, Shu XO, et al. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. British Journal of Cancer 2000;82:234–240. [PubMed: 10638995]
19. Perrillat F, Clavel J, Auclerc MF, et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. Br J Cancer 2002;86:1064–1069. [PubMed: 11953850]
20. Petridou E, Kassimos D, Kalmanti M, et al. Age of exposure to infections and risk of childhood leukaemia. Bmj (Clinical Research Ed) 1993;307:774.
21. Petridou E, Trichopoulos D, Kalapothaki V, et al. The risk profile of childhood leukaemia in Greece: a nationwide case-control study. British Journal of Cancer 1997;76:1241–1247. [PubMed: 9365177]
22. Roman E, Watson A, Bull D, Baker K. Leukaemia risk and social contact in children aged 0-4 years in southern England. J Epidemiol Community Health 1994;48:601–602. [PubMed: 7830017]
23. Rosenbaum PF, Buck GM, Brecher ML. Early child-care and preschool experiences and the risk of childhood acute lymphoblastic leukemia. American Journal of Epidemiology 2000;152:1136–1144. [PubMed: 11130619]
24. Schüz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. British Journal of Cancer 1999;80:585–590. [PubMed: 10408870]
25. van Steensel-Moll HA, Valkenburg HA, van Zanen GE. Childhood leukemia and infectious diseases in the first year of life: a register-based case-control study. American Journal of Epidemiology 1986;124:590–594. [PubMed: 3463201]
26. Roman E, Simpson J, Ansell P, et al. Childhood acute lymphoblastic leukemia and infections in the first year of life: a report from the United Kingdom Childhood Cancer Study. Am J Epidemiol 2007;165:496–504. [PubMed: 17182983]
27. Ma X, Does MB, Metayer C, Russo C, Wong A, Buffler PA. Vaccination history and risk of childhood leukaemia. Int J Epidemiol 2005;34:1100–1109. [PubMed: 15951359]
28. Mallol-Mesnard N, Menegaux F, Auvrignon A, et al. Vaccination and the risk of childhood acute leukaemia: the ESCALE study (SFCE). Int J Epidemiol 2007;36:110–116. [PubMed: 17227780]
29. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault GP. Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood Leukemia Study. Am J Epidemiol 2008;167:598–606. [PubMed: 18079130]
30. Kinlen L, Jiang J, Hemminki K. A case-control study of childhood leukaemia and paternal occupational contact level in rural Sweden. Br J Cancer 2002;86:732–737. [PubMed: 11875735]
31. Kinlen LJ. High-contact paternal occupations, infection and childhood leukaemia: five studies of unusual population-mixing of adults. Br J Cancer 1997;76:1539–1545. [PubMed: 9413937]
32. Kinlen LJ, Bramald S. Paternal occupational contact level and childhood leukaemia in rural Scotland: a case-control study. Br J Cancer 2001;84:1002–1007. [PubMed: 11286484]
33. Pearce MS, Cotterill SJ, Parker L. Fathers' occupational contacts and risk of childhood leukemia and non-hodgkin lymphoma. Epidemiology 2004;15:352–356. [PubMed: 15097020]
34. Fear NT, Roman E, Reeves G, Pannett B. Are the children of fathers whose jobs involve contact with many people at an increased risk of leukaemia? Occup Environ Med 1999;56:438–442. [PubMed: 10472313]

35. Fear NT, Simpson J, Roman E. Childhood cancer and social contact: the role of paternal occupation (United Kingdom). Cancer Causes Control 2005;16:1091–1097. [PubMed: 16184475]

36. Chang JS, Metayer C, Fear NT, et al. Parental social contact in the work place and the risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2007;97:1315–1321. [PubMed: 17923868]

37. Brown RC, Dwyer T, Kasten C, et al. Cohort profile: the International Childhood Cancer Cohort Consortium (I4C). Int J Epidemiol 2007;36:724–730. [PubMed: 17255350]

38. Mori H, Colman SM, Xiao Z, et al. Chromosome translocations and covert leukemic clones are generated during normal fetal development. Proc Natl Acad Sci U S A 2002;99:8242–8247. [PubMed: 12048236]

39. Wiemels JL, Cazzaniga G, Daniotti M, et al. Prenatal origin of acute lymphoblastic leukaemia in children. Lancet 1999;354:1499–1503. see comments. [PubMed: 10551495]

40. Gustafsson B, Bogdanovic G. Specific viruses were not detected in Guthrie cards from children who later developed leukemia. Pediatr Hematol Oncol 2007;24:607–613. [PubMed: 18092251]

41. Kosulin K, Haberler C, Hainfellner JA, Amann G, Lang S, Lion T. Investigation of adenovirus occurrence in pediatric tumor entities. J Virol 2007;81:7629–7635. [PubMed: 17494079]