INFECTIOUS DISEASES
AS A POTENTIAL RISK OF PEDIATRIC MALIGNANCIES
PREVENTION OF INFLUENZA-VIRUS INFECTION
IN CHILDREN DURING CHEMOTHERAPY
EPIDEMIOLOGICAL AND CLINICAL STUDIES

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PH.D. THESIS

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INTRODUCTION

Epidemiological studies:

A number of previous epidemiologic studies have suggested that infectious disease may be involved in the aetiology of childhood leukemia. Acute lymphoid leukaemia (ALL) is the most common type of cancer found in children and exposure to infections before or around birth may be associated with the risk of childhood ALL, but the findings are contradictory.

Previous studies reported that childhood acute lymphoblastic leukaemia can be linked with spatially heterogeneous environmental exposures. The presence of spatial clustering would be consistent with geographically localized environmental exposures over long periods of time.

Clinical study:

Seasonal influenza viruses and the pandemic influenza virus A (2009 H1N1) have caused significant morbidity and mortality around the world. In most patients, infection results in influenza-like symptoms without complications. In patients with cancer influenza infection can result in prolongation of chemotherapy and can cause serious complications, even death. A possible option to prevent influenza infection and its complications, is vaccination. After 2009, few studies investigated the immune response and safety of vaccines for the pandemic influenza virus A (2009 H1N1) in children with malignancy.

AIMS

The aim of our first study was to investigate the presence of spatial clustering in childhood ALL that might arise as a result of persistent and localized environmental exposures using an independent population.

To confirm the role of infectious aetiology in our second study the relationship between death from infectious disease of the respiratory system and the risk of ALL in children aged less than seven years was investigated.

In our prospective clinical study we evaluated the immune response and safety of concomittant trivalent-inactivated vaccine for seasonal influenza viruses (H1N1A, H3N2A and B), and monovalent-inactivated vaccine for the 2009 pandemic influenza virus A in children undergoing chemotherapy.

PATIENTS AND METHODS OF OUR STUDIES

I.1. Patients

The area considered was South Hungary which includes two regions—South Transdanubia and South Great Plain. Children born between 1981 and 2000 were considered. Births and cases were assigned to six county districts within the study area.

Registrations of first malignancies for children, born and diagnosed under age 5 years in Hungary before the end of 2005 were obtained from the Hungarian Paediatric Oncology Group (HPOG). The ALL registrations were based on address of residence of the family. Annual data on population of each settlement by gender in the study period were obtained from the Central Demographic Agency.

I.2. Statistical Methods

The Potthoff-Whittinghill (PW) and Moran I methods were used to test for spatial clustering and autocorrelation, respectively.

Analyses were performed at two levels of areal resolution, counties and settlements. There were 6 counties with 906 settlements in the spatial clustering analyses.

Statistical significance was taken as $p<0.05$ in all analyses. Similarly, the spatial distribution of cases in the study area was simulated to measure spatial autocorrelation index between the incidence rates in the geographical units using Moran I method.

II.1. Patients

The area considered was the same as in our first study. Children born between 1981 and2005 were considered. Registrations of first malignancies for children, born in South Hungary and diagnosed under age seven years in Hungary before the end of 2010 were obtained from the Szeged and Pécs centres of Hungarian Paediatric Oncology Group (HPOG).

The gender, year and county district of birth of all live birth registrations in the study period were obtained from the Central Demographic Agency.

Both deaths from influenza (ICD9: 487, ICD010: J10-J11), deaths from chronic bronchitis (ID9: 490-496, ICD10 J41-J42) and deaths from pneumonia (ID9: 480-486, ICD10 J12-J18) were considered as exposures since the former were rare. From published statistics on infectious deaths data were abstracted on: number of cases of influenza in Hungary and annually

total number of cases of influenza by county districts, hence the numbers of male and female flu cases in each county district in each year were calculated.

II.2. Statistical methods

Poisson regression was used to investigate the relationship between risk of cancer and measure of community infections (e.g.: number of deaths in respiratory diseases, which includes flu).

III.1. Patients

We enrolled 1 to 18-year-old children receiving chemotherapy for various types of cancer at the Pediatric Oncohematology Units of the University of Pécs and Semmelweis University of Budapest, from November to December, in the years 2009 and 2010. The children enrolled for the study were the consecutive patients treated in the respective centers. We exluded children with a recent history of 2009 pandemic A vaccination, confirmed diagnosis of the pandemic influenza A (2009 H1N1) virus infection prior to the vaccination, and past history of allergy to eggs, as well as those who were receiving other vaccines during the study period.

III.2. Methods

Vaccine and Schedule

In 2009, the pandemic vaccine (Fluval P -Omninvest, Pilisborosjeno, Hungary) was a monovalent vaccine, the seasonal influenza vaccine (Fluval AB7 – Omnivest) was a trivalent inactivated whole-virion influenza vaccine. In 2010, a polyvalent vaccine containing both the seasonal and the pandemic strains was produced by a method which met the requirements of the European Agency for the Evaluation of Medicinal Products for interpandemic influenza vaccines.

Vaccination schedule was determined according to the recommendations of the Infectology Department of the Hungarian National Healthcare Advisory Board, based on data from the National Center of Epidemiology, Budapest, Hungary. Vaccination was performed 3-4 weeks after the last chemotherapy administration, and at least two days before the next chemotherapy treatment.

Sample Collection and Serologic Analysis

Once informed consent was obtained, a 3 mL blood sample was taken from each participant before vaccination and another 3-4 weeks afterwards, mostly via central venous catheter. The

serum was separeted by centrifugation, then immediately frozen and stored at -80 ˚C until the laboratory measurements on haemaglutination-inhibition (HAI) antibody titres were performed. All serologic tests were done at a single central laboratory (Department of Virology, National Center of Epidemiology, Budapest, Hungary). All paired sera were tested in duplicate on the same day using identical reagents. Seroprotective titer was defined as having a HAI antibody titer ≥40, and seroresponse was defined as having a fourfold or greater increase in HAI antibody titers after vaccination. Before vaccination, and on day 21-28, blood samples were taken for haemagglutination-titer, immunoglobulin level and white blood cell count.

Adverse Reactions and Medical Conditions

Baseline assessments on day 0 included demographic data, medical history, and physical examinations were done. We checked all patients at least weekly by physical and laboratory (complete blood count) examination during the follow-up period, which lasted until the final blood collection for serologic study. Possible vaccine-related adverse events were monitored. On day 21–28, standard medical history and medications used during the days since the last visit were summerized, and physical examination was done before blood samples were collected. Safety variables were collected at follow-up visits through patient history and physical examination.

Statistical Analysis

Data were analyzed using paired and Student t-tests, chi-square-test (or Fisher exact-test) in the univariate analysis. Then the mixed model was applied to investigate the relationship between the outcome of vaccination (seroprotection / seroconversion) and the measured factors (immunoglobulin level, lymphocyte count, age).

RESULTS OF OUR STUDIES

There were 134 cases 73 (54.5 %) boys and 61 (45.5 %) girls) of ALL in those aged 0–4 years in South Hungary in the spatial clustering study. Eight cases (five boys and three girls) of ALL were diagnosed before the age of 1 year. There were 547,034 live births in the study area during the 20 year-interval of 1981–2000. The overall incidence rate of ALL was 4.90 per 100000 person years for children aged 0–4 years. The highest incidence rates of 6.79 per 100000 person years and 6.41 per 100,000person years were found in western counties of South Hungary.

The incidence rate of boys (5.21 per 100000 person years) was non-significantly higher than the incidence rate of girls (4.57 per 100000 person years). The female incidence rates varied from 2.81 to 5.27 per 100000 person years, and the male incidence rates varied from 3.63 to 8.30 per 100000 person years between counties.

We found a statistically significant spatial clustering for all cases within smaller settlements which was attributable to clustering of male cases.

The highest observed incidence rates of ALL at settlement level were 6.29 and 5.38 per 1,000 persons in Baranya and Somogy counties between 1996 and 2000, respectively.

A significant spatial autocorrelation was found in the incidence of ALL for all cases in the Moran analysis (I=0.18, p=0.0012) over the whole period. The global Moran (I=0.14) statistic was significant (p=0.028) among boys, but non significant among girls (I=0.04, p=0.16).

In our second study the total numbers of deaths were during the 20 year 26753, 5649 and 770 from chronic bronchitis, pneumonia and influenza, respectively. The median mortality rate of chronic bronchitis was 815.8 / 100000 person years (inter quartile range (IQR): [511.5–1280.1]/ 100000 person years), of pneumonia was 176.1/ 100000 person year (IQR: [144.0–232.6] / 100000 person year, and of influenza was 22.6 / 100000 person year (IQR: [18.5–37.7] / 100000 person year).

The study included 176 cases 92 (52.3%) boys and 84 (47.7%) girls) of ALL in those aged 0-6 years in South Hungary. Eight cases (five boys and three girls) were diagnosed before the age of 1 year. There were 547.034 live births in the study area during the 20 year-interval of 1981-2000. The overall incidence rate of ALL was 5.37 per 100,000 person years for children aged 0-6 years. The incidence peak age at diagnosis of ALL was 2-5 years.

There was a moderate risk of ALL disease exposed around birth to higher levels of mortality of the chronic respiratory diseases among children aged 2-5 years (p=0.035) and aged 2-6 years (p=0.033). We found a significant trend for risk of ALL disease exposed around birth to higher levels of mortality of pneumonia among children aged 2-5 years (p=0.010) and aged 2-6 years (p=0.025). On the other hand these trends were significant only in girls (p=0.08), not in boys. Nevertheless, significantly increased risk of childhood ALL was detected among children under one year of age exposed around the birth to higher levels of mortality from influenza (OR for trend was 1.05; 95%CI [1.01 – 1.10]; p=0.012). This increased risk was detected in girls (OR: 1.22; 95% KI [1.05 – 1.42]; p=0.009) , but not in boys (OR=0.91; 95% KI [0.65 – 1.26]; p=0.56).

In our clinical investigation twenty-seven pediatric patients with cancer (15 males and 12 females) completed the study. Their median age was 10.4 years (range 2.83 – 18.16 years). The underlying diseases were leukemia (10 patients), lymphoma (2 patients), and solid tumor (15 patients). Fourteen patients were younger than 10 years old, and therefore received 0.25 mL of vaccine, while the remaining thirteen patients received 0.5 mL of vaccine. All 27 patients received chemotherapy within 1 month before vaccination, and all continued to receive scheduled chemotherapy after vaccination. Five were undergoing maintenance therapy. The remaining twenty-two were receiving intensive cytostatic treatment. In the latter cases, cytostatic treatment was administered only on the 3rd day after vaccination.

Prevaccination seroprotective rates were significantly higher for seasonal influenza viruses H1N1 and H3N2, than for seasonal B and pandemic H1N1Swl ($p<0.001$). The differences between pre- and post-vaccination seroprotective rates in the case of Influenza B was significant ($p=0.038$). No significant differences were found between pre- and post-vaccination seroprotective rate changes with other viruses (H1N1Swl $p=0.064$, H1N1 $p=0.277$, H3N2 $p=0.160$). We compared the pre- and post-vaccination seroprotective rate changes and seroresponse rate of each seasonal Influenza virus with the pandemic H1N1Swl virus by a paired t-test. Neither HAG seroprotective rate changes, nor seroconversion for seasonal H1N1-H1N1Swl, H3N2-H1N1Swl, B-H1N1Swl were significant using this method.

Comparing the effect on seroprotection change and seroconversion of each virus type combined with age category (over and below 10 years) using binary logistic regression, here was no significant difference either in seroprotection rate changes or in seroconversion, between the different influenza virus strains. Lymphocyte counts at the time of vaccination were between 0.44 G/l and 7.77 G/l (median: 1.34 G/l). Lymphocyte count above 1.0 G/l was significantly correlated with immune response after influenza vaccination ($p=0.018$). On the other hand, lymphocyte count above 1.0G/l did not have a significant influence on seroprotection change. These results were independent of virus strain. The immunoglobulin G (IgG) levels at the time of vaccination were between 4.27 g/l and 12.8g/l (median: 7.32 g/l). Most (14/19) of the patients, had age related normal level of IgG at the time of vaccination. This was significantly correlated with immune response after influenza vaccination, independently of virus strain ($p=0.01$). Age related normal IgG level did not

have a significant influence on seroprotection change (p=0.063). Type of malignancy and status of cancer therapy (maintenance or intensive treatment) did not significantly influence seroprotection change or seroconversion. There were no breakthrough influenza infections, and neither of the non-vaccinated patients suffered from influenza during this period.

Adverse Reactions

We recorded no local adverse reactions (e.g. injection site induration, erythema, swelling, or warmth). One case of malaise (3.7%) was detected on the day after vaccination. No medical intervention was necessary. No vaccine related serious adverse events were observed.

DISCUSSION

In our first epidemiological study, significant spatial clustering for all cases at the smaller settlement level was found which was attributable to clustering of male cases. This finding partly confirms our previous results where different pattern of risk to acute lymphoid leukaemia was found in boys and girls aged less than 5 years and was attributable to an association between the risk of childhood leukaemia and population mixing, which has been interpreted as evidence of an infectious aetiology. South Hungary, the area considered, covers nearly a quarter of the childhood population of the country providing a representative sample of Hungarian children. Thus, our study included a large sample of a population over a 20 year period of time.

It is important to note that the spatial clustering found amongst children could have arisen by chance or it could be explained by lifestyle factors, characteristics of the residential area or another unmeasured heterogeneous geographical factor. However, the applied clustering analyses have used an optimal statistical method for detecting the global occurrence of localized aggregations of cases. As far as we are aware, this was the first epidemiological study reporting the effect of spatial clustering of ALL for boys and girls separately.

Our second study included a large sample of a population over a 20-year period of time. In our study the peak of childhood leukemia cases diagnosed less than seven year were selected to analyze infectious effects on developing ALL. In spite of the apparent limitation of our study that we have not had data of other infectious agents, including measles, chicken pox, and adenovirus and we have applied an indirect measurement on influenza, this 20-year long study support new evidence to understand the different pattern of female and male childhood ALL cases.

The purpose of our clinical study was to investigate the efficacy and safety of concomittant trivalent-inactivated vaccines for seasonal influenza viruses (H1N1A, H3N2A, and B), monovalent-inactivated vaccine for the 2009 pandemic influenza virus A, and a combined (pandemic and seasonal vaccine - polyvalent) vaccine in 2010, in children with cancer undergoing chemotherapy. Vaccinations (H1N1A, H3N2A, B and pandemic H1N1Swl) produced no significant adverse events, but resulted in limited serosresponse rates (22%, 37%, 22% and 30% respectively). These results were similar to response rates reported earlier for influenza viruses, and recently for pandemic influenza virus A. Our patients were receiving chemotherapy at the time of vaccination, thus limited seroprotection changes and serosresponse rates were expected. The proportion of patients achieving protective antibody levels to individual viral strains following vaccination has been reported to be 29%–75% in children on chemotherapy. In the present study all children were receiving chemotherapy, and an immune response was observed in 22%–37% of children. There was no significant difference in either post-vaccination seroprotection change or seroconversion of the different seasonal influenza
viruses when compared with the pandemic H1N1Swl virus, results similar to those obtained in healthy people. There is contraversial data regarding lymphocyte count, and serum IgG level, as factors responsible for immune response after administration of influenza vaccine in children with cancer undergoing chemotherapy. The present study demonstrates that, for both seasonal viruses and the pandemic H1N1 virus, lymphocyte count above 1.0 G/l, and normal IgG level has significant influence on the immune response after vaccination.

SUMMARY OF THE NEW FINDINGS PRESENTED IN THE THESIS

1. We found a statistically significant spatial clustering in childhood ALL in South-Hungary for all cases within smaller settlements which was attributable to clustering of male cases.
2. To our knowledge we proved at first a gender-difference in spatial clustering in childhood ALL.
3. We described a significant association between incidence of ALL among children aged 2-5 years (incidence peak population of childhood ALL) and mortality of the chronic respiratory diseases and pneumonia.

4. We could have determined a significantly increased risk of ALL among infants exposed around the birth to higher levels of mortality from influenza.
5. We could have determined the safety of concurrently given pandemic H1N1 and seasonal Infuenza vaccine in children during chemotherapy.
6. We proved no difference between seasonal and pandemic Influenza vaccination neither in HAG seroprotective rate changes, nor in seroconversion rates.
7. We showed that in chemotherapy treated children lymphocyte count above 1.0 G/l is significantly correlated with immune response after influenza vaccination.
8. We observed that in chemotherapy treated children age related normal level of IgG at the time of vaccination significantly correlated with immune response after influenza vaccination.

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The thesis is based on the following papers and abstract:

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