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Association between infectious burden, socioeconomic status, and ischemic stroke

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ABSTRACT

Background and aims: Infectious diseases contribute to stroke risk, and are associated with socioeconomic status (SES). We tested the hypotheses that the aggregate burden of infections increases the risk of ischemic stroke (IS) and partly explains the association between low SES and ischemic stroke.
Methods: In a case–control study with 470 ischemic stroke patients and 809 age- and sex-matched controls, randomly selected from the population, antibodies against the periodontal microbial agents *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, against *Chlamydia pneumonia*, *Mycoplasma pneumoniae* (IgA and IgG), and CagA-positive *Helicobacter pylori* (IgG) were assessed.
Results: IgA seropositivity to two microbial agents was significantly associated with IS after adjustment for SES (OR 1.45 95% CI 1.01–2.08), but not in the fully adjusted model (OR 1.32 95% CI 0.86–2.02). By trend, cumulative IgA seropositivity was associated with stroke due to large vessel disease (LVD) after full adjustment (OR 1.88, 95% CI 0.96–3.69). Disadvantageous childhood SES was associated with higher cumulative seropositivity in univariable analyses, however, its strong impact on stroke risk was not influenced by seroepidemiological data in the multivariable model. The strong association between adulthood SES and stroke was rendered nonsignificant when factors of dental care were adjusted for.
Conclusions: Infectious burden assessed with five microbial agents did not independently contribute to ischemic stroke consistently, but may contribute to stroke due to LVD. High infectious burden may not explain the association between childhood SES and stroke risk. Lifestyle factors that include dental negligence may contribute to the association between disadvantageous adulthood SES and stroke.

1. Introduction

Stroke, especially ischemic stroke (IS), is a multifactorial disease with numerous contributing risk factors. These risk factors are target of preventive strategies attempting to mitigate the future burden of stroke. Current risk factor models may explain about 90% of ischemic stroke occurrence [1]. However, some epidemiological aspects of stroke may not be sufficiently explained yet [2–4].

Infectious and inflammatory diseases, as well as unfavorable socioeconomic conditions have been described as contributors to the risk of stroke [4–7]. Different chronic infections have been found to be associated with stroke, including clinical periodontitis, infections with the periodontal pathogens *Porphyromonas gingivalis* (Pg) and *Aggregatibacter actinomycetemcomitans* (Aa), infections with *Helicobacter pylori* (Hp), and particularly with *Hp* strains carrying the cytotoxin-associated gene A (CagA) [8–11]. *Chlamydia pneumonia* (Cp), *Mycoplasma pneumonia* (Mp), and *Legionella pneumophila* (Lp) are as well among those microbial agents whose link with stroke has been discussed [12]. However, the results of

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studies investigating single agents are ambiguous [13]. A current hypothesis suggests that the aggregate burden of microbial agents to which an individual has been exposed to during his or her whole lifetime, rather than single pathogens, increases the risk of stroke ("infectious burden concept") [5]. In a recent analysis of the Northern Manhattan Study, no association was found between the risk of stroke and any of the five serologies to common infections (Cp, Hp, Cytomegalovirus, Herpes Simplex Virus 1 and 2). However, a derived infectious burden index showed an association with stroke [14].

Socioeconomic status (SES) is negatively associated with the risk of stroke [15]. In a case-control study, we recently showed that SES during childhood and adulthood are each independently linked to stroke risk [16]. Several chronic infectious diseases such as periodontitis and infection with *Hp* are more common in people with disadvantageous social conditions [17]. Thus, it seems likely that chronic infections contribute to the association between socioeconomic conditions and stroke, together with other factors such as a health neglecting lifestyle.

Based on the data from the same case-control study, we tested the hypotheses that the infectious burden (=aggregate number of seropositivities to selected infectious agents) is associated with the risk of IS and that chronic infections and elements of a health neglecting lifestyle contribute to the association between SES during childhood, adolescence, and adulthood and the risk of IS.

2. Patients and methods

The "GENESIS" study is a case-control study with 470 first-ever ischemic stroke (FEIS) cases (40% women, mean age 66.5 ± 10.8 years; 60% men, 65.5 ± 10.7) and 809 age- and sex-matched controls (41.8% women, 66.4 ± 11.1; 58.2% men, 67.9 ± 9.5), randomly selected from the general population. The target population consists of individuals aged 18–80 years, living in the city of Ludwigshafen am Rhein in South-West Germany. „GENESIS" was established within the framework of the Ludwigshafen Stroke Study (LuSST), a population-based stroke registry that started on January 1st, 2006, using standard definitions and multiple overlapping methods of case-ascertainment in order to identify all cases with incident stroke or transient ischemic attack among the population of Ludwigshafen (163.340 inhabitants on December 31, 2009). A detailed description of LuSSt and the „GENESIS" study have been published recently [16,18]. The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (837.333.05(4991)).

2.1. Inclusion and exclusion criteria

Inclusion criteria besides age and permanent residency in the study area were Caucasian ethnicity and written informed consent to study participation. Inclusion criterion for cases was the diagnosis of a FEIS based on an acute neurological deficit lasting >24 h with no other reason than cerebral ischemia. All cases received a cerebral CT or MRI. Exclusion criteria for both cases and controls included any previous stroke, myocardial infarction within 90 days, dementia, severe aphasia, insufficient understanding of the German language or any other relevant communication barrier and severe disability that precludes interview participation.

2.2. Recruitment

For recruitment of controls, a random sample of Ludwigshafen residents was drawn from the population registry including name, age, sex and address. Subsamples were consecutively taken to match the age and sex distribution of cases. Those selected received invitation letters with detailed information on the study and request for their participation. The participation rate for controls was 46.6%. The cases included incident stroke cases from the LuSSt registry. According to the study protocol only in-patients at the Klinikum Ludwigshafen were asked for participation in "GENESIS", since only few patients in the area did not attend this hospital. This group represents about 89% of all cases in LuSSt. The participation rate for cases was 73.7%.

2.3. Data collection and laboratory tests

Cases and controls were interviewed by trained interviewers using a standardized questionnaire. We collected data on age, sex, anthropometric measures, previous diseases, and previous visits to a dentist as markers of health behavior, number of teeth, smoking, alcohol intake, physical activity, dietary patterns, medication and social history. In both, cases and controls, blood pressure was measured after 5 min of resting, a 12-lead electrocardiogram and a Duplex-sonography of brain supplying arteries were performed. Venous blood samples were taken in cases and controls.

Serum was separated by low-speed centrifugation and stored at −70 °C until analysis. Serum levels of IgA and IgG antibodies against *Aa* and *Pg* were determined by multi-serotype-ELISA as previously described [19]. Serum levels of IgG antibodies against *Hp* and of IgG and IgA antibodies against *Cp* and *Mp* were assessed by using commercial enzyme immunoassays (Enzygnost® and Novagnost® Siemens Healthcare) at the Institute of Clinical Chemistry, Klinikum Ludwigshafen.

2.4. Definition of variables

Cardiovascular risk factors were defined according to current national and international guidelines and have been described in detail [20]. A detailed presentation of the SES measures has been published recently [16]. Etiological subtypes of IS were ascertained using modified TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment) as previously described [20]. The category "large vessel disease" (LVD) included "probable atherothrombotic stroke" (AT) and stroke due to "large artery atherosclerosis" (LAA). In 159 cases, etiology of IS was classified as LVD (19.7% of all cases).

2.5. Statistical analysis

We report absolute and relative frequencies of risk factors, SES and seropositivities to infectious agents by case–control status. Infectious burden was calculated as cumulative IgA-positivity, cumulative IgG-positivity, and aggregated IgG/IgA-positivity. Odds ratio (OR) estimates and 95% confidence intervals (CI) are presented based on conditional logistic regression models, conditioned on age (2-year-age groups) and sex, and adjusted for risk factors, SES, and the respective other infection indicators. Associations between the number of seropositivities to infectious agents and SES in childhood, adolescence, and adulthood were investigated by the Jonckheere-Terpstra trend test. To control for a potential bias owing to a lower response of controls from more disadvantaged social background, we performed a sensitivity analysis, comparing school education data in our control group with those of the general population received from the municipal statistical office. Although individuals with low school education were moderately underrepresented in our control group, results regarding socioeconomic factors as stroke risk factor were altered only to a minor degree by adjustment for a differential response rate in controls [16]. For all analyses, the statistical software R was used, conditional logistic regression estimates were obtained through the R package survival, the Jonckheere-Terpstra trend test