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Predicting the risk of atherosclerosis in patients with cystic fibrosis – rationale and design of a prospective cohort study

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ABSTRACT

The project "Risk of atherosclerosis in cystic fibrosis in relation to the exogenous and endogenous factors that influence the course of the disease" ranked first in the OPUS2 Competition, as announced in May 2012 by the Polish National Science Center. The total value of the grant is 198,580 PLN (ca. 50,000 EUR). The grant was awarded jointly to the Department of Pediatric Gastroenterology and Metabolic Diseases and to the Department of Cardiac Intensive Care at Poznan University of Medical Sciences, Poland. The project will be focused on conducting a prospective cohort study in patients with cystic fibrosis (CF) and healthy controls. Cases of symptomatic and asymptomatic forms of coronary heart disease in patients with CF were reported [1, 2]; however, no data on the epidemiology of atherosclerosis in patients with CF were published so far. In the past, cardiovascular disease in patients with CF used to be limited to pulmonary heart disease as a consequence of end-stage chronic obstructive pulmonary disease [3]. Although hypertension has not yet been officially recognized as a major problem in this population [4], there are reports indicating that it is found in 20% of patients in adult CF care centers [5]. The project is innovative in nature and necessitates close co-operation between cardiology and basic science units.

Keywords: atherosclerosis, cystic fibrosis, coronary heart disease.

General information

The project "Risk of atherosclerosis in cystic fibrosis in relation to the exogenous and endogenous factors that influence the course of the disease" ranked first in the OPUS2 Competition, as announced in May 2012 by the Polish National Science Center. The total value of the grant is 198,580 PLN (ca. 50,000 EUR). The grant was awarded jointly to the Department of Pediatric Gastroenterology and Metabolic Diseases and to the Department of Cardiac Intensive Care at Poznan University of Medical Sciences, Poland.

The project will be focused on conducting a prospective cohort study in patients with cystic fibrosis (CF) and healthy controls. Cases of symptomatic and asymptomatic forms of coronary heart disease in patients with CF were reported [1, 2]; however, no data on the epidemiology of atherosclerosis in patients with CF were published so far. In the past, cardiovascular disease in patients with CF used to be limited to pulmonary heart disease as a consequence of end-stage chronic obstructive pulmonary disease [3]. Although hypertension has not yet been officially recognized as a major problem in this population [4], there are reports indicating that it is found in 20% of patients in adult CF care centers [5].

The project is innovative in nature and necessitates close co-operation between cardiology and basic science units.

The Basic Concept of the Research

Epidemiological data indicate that risk factors for cardiovascular disease observed among children, adolescents and young adults have a prognostic significance for adulthood [6]. CF guidelines that can be found in the January 2004 Consensus Report were designed to help with the transition of CF health care from pediatricians to internists or other adult care providers. Many aspects of cardiovascular disease other than pulmonary heart disease, e.g. hypertension, are missing from this consensus report [7]. There is a need to continually update and extend our knowledge of aging-related diseases in CF patients [8]. The fact that cases of asymptomatic and symptomatic coronary artery disease have been reported in association with CF suggests that life expectancy in adult CF patients has reached sufficient length so as to make artery disease a concern. This also illustrates the need to perform systematic research in this area [9, 10].

Research Project Objectives

The purpose of the project is to evaluate the risk of atherosclerosis in CF patients in relation to the exogenous and endogenous factors that influence the course of the disease. Early (subclinical) risk factors of atherosclerosis will be evaluated. In addition, the academic significance of the project is strengthened by its potential to identify the relationship between atherosclerotic changes and genetics, as well as organ-specific and systemic CF-related pathology.

Research Methodology

Study Population

The study will enroll patients with CF. The control group will consist of 50 healthy volunteers matched to CF patients according to gender and age. The written consent to participate in the study will be obtained from all entrants and, in cases of underage study participants, also from their parents. The summary of inclusion and exclusion criteria is shown in **Table 1**.

Methods

In all examined patients the following parameters characterizing the clinical expression of disease will be assessed:

1. Nutritional status – using typical anthropometric parameters: standardized body height and weight (Z-score), standardized body mass index (BMI Z-score), and a biochemical parameter – serum albumin concentration;
2. Diet – using a 7-day consumption questionnaire and calculations performed using "Dietician" software;
3. Lung function – using spirometry (FEV1 – forced expiratory volume in 1 second – expressed as a percentage of predicted value);
4. Respiratory tract colonization by Pseudomonas aeruginosa – based on the results of sputum culture;
5. Exocrine pancreatic function – based on the measurement of elastase-1 concentration in feces;
6. Parenchymal liver damage and cholestasis (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase).

   In addition, detailed information concerning:
   - the supplementation of pancreatic enzymes,

Table 1. Inclusion and exclusion criteria for patients with cystic fibrosis (CF) and healthy subjects

Cystic fibrosis group	Control group
Inclusion criteria: 1. CF diagnosed based on medical history confirmed by the molecular analysis of mutations in the CFTR gene, clinical picture, elevated concentrations of chloride anions in sweat 2. Age >16 years 3. Consent to participate in the study.	Inclusion criteria: 1. Age >16 years 2. Consent to participate in the study.
Exclusion criteria: 1. Positive family history of dyslipidemia (hypercholesterolemia, hypertriglyceridemia), 2. Early episodes of coronary artery disease and cerebrovascular diseases in the family (occurrence of episodes of the disease before the age of 65 years in women and before 55 years in men).	Exclusion criteria: 1. Positive family history of dyslipidemia (hypercholesterolemia, hypertriglyceridemia), 2. Early episodes of coronary artery disease and cerebrovascular diseases in the family (occurrence of episodes of the disease before the age of 65 years in women and before 55 years in men).

- inhaled or oral antibiotics taken permanently,
- the last oral and intravenous antibiotic-therapy will be collected.

In all study participants (CF and control groups) the following parameters related to the prediction of the risk of atherosclerosis will be assessed using enzyme-linked immunosorbent assay (ELISA): adhesion proteins (sP-selectin, vascular cell adhesion molecule-l), asymmetric dimethylarginine, apolipoprotein E, adiponectin, oxidized low-density lipoprotein, high sensitivity C-reactive protein. Apolipoproteins A-1 and B will be estimated using the turbidimetric method. The lipid profile (total cholesterol, triglycerides, high density lipoproteins and low-density lipoproteins) will be assessed using the enzymatic colorimetric method.

The assessment of vascular changes will involve a non-invasive measurement of carotid intima media thickness (CIMT) in all the study participants (using high-resolution ultrasound system equipped with a linear head) and an analysis of vascular stiffness (50 CF patients; 30 healthy volunteers). The latter will be evaluated on the basis of two parameters: the speed of pulse wave assessed using photoplethysmography and the analysis of pressure waveforms and central hemodynamics using commercial equipment.

Expected Results

The project will improve the understanding of the course of atherogenesis in patients with CF, a topic on which no specific studies were published so far. It is expected that the results will shed light on the role of both exogenous and endogenous determinants of atherosclerosis in patients with CF. The study will provide new information regarding the atherosclerotic process in nonobese individuals, who have often been neglected in the studies of atherosclerosis as a low risk group. In the future, the newly obtained insight might translate to improved medical care in CF patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest in the authorship or publication of contribution.

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