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Factors Associated with Frontotemporal Dementia in China: A Cross-Sectional Study

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Background and Aims. There is a growing focus on frontotemporal dementia (FTD). However, compared with other major dementias, very little is known about the factors associated with FTD. The present study evaluated candidate factors associated with FTD in the Chinese population.

Methods. One hundred eight elderly patients (36 diagnosed with FTD and 72 controls) of the Neurology Central Hospital of Tianjin (China), were diagnosed by neurologists, and recruited for the study between November 2011 and November 2014. Clinical evaluation, laboratory tests, brain images (computed tomography scans and magnetic resonance images), neuropsychological, and neuropsychiatric assessments were performed. The association between FTD and the variables was assessed using multiple binary logistic regression analyses adjusted for age and gender.

Results. With controls as the reference category, education was associated with the diagnosis of FTD (adjusted odds ratio [OR], 1.60; 95% confidence interval [CI]: 1.17–2.19). Serum vitamin B_{12} levels were associated with the diagnosis of FTD (adjusted OR, 0.99; 95% CI: 0.98–0.99). Serum low-density lipoprotein (LDL) levels were associated with the diagnosis of FTD (adjusted OR, 8.54; 95% CI: 2.86–25.49).

Conclusions. Education and serum LDL levels were positively associated with the diagnosis of FTD. Serum vitamin B_{12} levels were negatively associated with the diagnosis of FTD.

Key Words: Education, Low-density lipoprotein, Vitamin B_{12}, Neurological disorders, Frontotemporal dementia.

Introduction

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous syndrome characterized by a progressive decline in behavior or language functions. This kind of dementia is associated with degeneration of the frontal and temporal lobes (1). Vieira et al. (2) estimated in a study aimed to review the prevalence and etiology of early-onset dementia by comparing early-onset dementia with senile dementia as well as to show the main causes of early-onset dementia and their prevalence. FTD is the third most common form of dementia across all age groups after Alzheimer's disease (AD) and Lewy body dementia and is a leading type of early-onset dementia. Although there is a great variability, onset of FTD symptoms typically occurs in individuals who are in their late 50s or early 60s (3,4). In patients <60 years, FTD is equal to or greater than AD in incidence (5). Differential diagnosis of FTD needs a careful history that examines the progression of behavioral changes, family history, behavior in face-to-face interviews, performance on neuropsychological testing, laboratory studies, and neuroimaging (6). Appropriate treatment of FTD requires an individually tailored

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approach. However, treatment of FTD, at present, is largely symptomatic (5). Therefore, the risk factors and pathogenesis of FTD should be further studied. Bang et al. indicated vitamin B_{12} concentration should be examined in the diagnostic process of FTD (6). Other studies indicated that folate and homocysteine (Hcy) may be risk factors for AD and other dementias (7,8). Borroni et al. (9) found patients diagnosed with FTD showed a higher level of education than patients diagnosed with AD. In the present work we aimed to examine the possible factors associated with FTD such as vitamin B_{12}, education, and other biochemical factors.

Subjects and Methods

FTD Patients and Control Volunteers

Between November 2011 and November 2014, 108 study subjects (36 diagnosed with FTD and 72 control volunteers) were recruited at the Neurology Central Hospital of Tianjin, China; 1:1 pair-wise matching is most often used. In theory, a case can be matched to a number of controls; however, when more than matched 1:4, the statistical efficiency will not increase significantly accompanied by the increased workload. Due to the limited number of cases and sufficient number of controls, all patients and control subjects were included and excluded by neurologists and matched 1:2 for age ($\pm$3 years) and sex in this study. All subjects underwent extensive examinations and behavioral assessments by trained neurologists. Patients with FTD met the following criteria for study inclusion: a) clinical diagnosis according to prior clinical consensus criteria for FTD (4,10) and b) neuropsychological confirmation of frontal lobe dysfunction. Diagnosis of FTD was based on medical and family histories, age of onset of dementia and neurological examination. All patients displayed characteristic features according to magnetic resonance imaging and CT. Carbon-11-Pittsburgh compound B-PET and fluorodeoxyglucose-PET were performed on cases for whom clinical diagnosis was uncertain after multidisciplinary team conference review. The stage of dementia was evaluated by means of the Mini-Mental State Examination (MMSE) (11) and Clinical Dementia Rating (CDR) scale (12). In addition, patients were asked to report whether they had any difficulty with 20 activities of daily living (ADL) (13). Patients met the following criteria: MMSE score 3.0−24.0 points (11); ADL score $\geq$22.0 (14); CDR scored 1−2 (12). Exclusion criteria were as follows: a) cerebrovascular disorders; b) history of schizophrenia, delusional disorder, or mood disorder with psychotic features or mental retardation according to DSM-IV criteria, and c) absence of a knowledgeable subject who could properly report on the patient's behavior.

Inclusion criteria for the control group were as follows: no serious physical disease, ability to complete the neuropsychological tests, and absence of any known neurological disorder or cognitive impairment, with an MMSE score $>$24.0 in controls with $\leq$6 years of education, or $>$26.0 with $>$6 years of education. Exclusion criteria were as follows: a) personal and familial (first-degree relatives) histories of neurological or psychiatric conditions and b) organic disease involving the central or peripheral nervous system.

Patients and controls were excluded if they were taking medications that alter folate, vitamin B_{12}, Hcy, total cholesterol (TC), triglyceride (TG), fasting plasma glucose (Glu), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) concentrations within the 2 months before baseline.

Socioeconomic, Clinical, and Anthropometric Assessments

We used semi-structured interviews of patients and informants in collecting data on the variables included in the study. Data collected included number of years of education, weight (kg), height (m), marital status (married/divorced or widowed), smoking status (yes/no), drinking status (yes/no), comorbid disease (heart disease, hypertension, cerebral infarction, diabetes, thyroid disease, Parkinson's disease, gatism, traumatic brain injury; yes/no), and family history of dementia (first relative degree, yes/no). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Blood Sampling and Analytical Methods

On the morning following the admission to the hospital, blood samples were drawn via vein puncture after at least a 12-h fast. Three blood tubes were collected from each patient. One contained the anticoagulant ethylenediaminetetraacetic acid (EDTA) and the others contained a coagulant. The tube containing EDTA was immediately centrifuged at 2,500 g for 10 min at 4°C. Plasma samples were then obtained and stored frozen at −80°C for subsequent measurement of Hcy. The two tubes that contained the coagulant were centrifuged at 3,000 g for 10 min, and the serum samples were obtained. In addition, a portion of each serum sample was stored frozen at −80°C for the subsequent measurement of serum folate, vitamin B_{12}, TC, TG, fasting plasma Glu, LDL, and HDL. Serum folate and vitamin B_{12} levels were measured using an automated immunoassay analyzer (Abbott AxSYM system, Abbott Laboratories, Abbott Park, IL) (15,16). Plasma levels of Hcy were measured using high-performance liquid chromatography (HPLC) as described by Poirier et al. (17). The levels of TC, TG, and Glu were determined by enzymatic methods (Human Diagnostics, Wiesbaden, Germany), and the levels of LDL and HDL were measured using homogeneous assays (Sekisui Medical Co., Japan) (18).