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Research paper

Insulin resistance as estimated by homeostasis model assessment predicts incident post-stroke depression in Chinese subjects from ischemic stroke

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ABSTRACT

Objective: Previous studies suggested that insulin resistance (IR) may be a significant causal risk factor for cardiovascular events and depression independent of other risk factors. In this prospective, we assess the value of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) at admission to predict post-stroke depression (PSD) later developed at 3 months follow-up.

Methods: This prospective, multicenter cohort study was conducted from January 2015 through December 2016 in China. Clinical information and HOMA-IR was assessed at admission. Neurological and neuropsychological evaluations were conducted at the 3-month follow-up.

Results: In the study population, 56.6% were male and the median age was 59 years (interquartile range [IQR]: 51–69). One hundred and eighty-six patients (26.6%) showed depression at 3 months after admission and in 53 patients (28.5%) this depression was classified as severe. For each 1-unit increase of HOMA-IR, the unadjusted and adjusted risk of PSD increased by 63% (odds ratios [OR]: 1.63; 95% confidence interval [CI]:1.44–1.85; $P < 0.001$) and 27% (1.27; 1.13–1.39; $P = 0.002$). In a multivariate model using the fourth quartiles of HOMA-IR vs. quartiles 1 through 3 together with the clinical variables, the marker displayed prognostic information (PSD: OR for fourth quartile, 2.76 [95% CI, 1.66–3.73; $P = 0.003$]).

Conclusions: The data suggests that the HOMA-IR may be of potential clinical relevance in identifying stroke patients at risk of developing depression, independent of the well-established predictors.

1. Introduction

Insulin resistance (IR) is a determinant of free fatty acids in the blood, which are in turn important in tryptophan metabolism and brain serotonin concentrations (Ladea et al., 2013). Previous observational epidemiological studies suggest that IR may be a significant causal risk factor for stroke (Bonora et al., 2007; Jeppesen et al., 2007; Thacker et al., 2011) and other cardiovascular events (Laakso et al., 2014; Paneni et al., 2014), independent of other risk factors.

Brain IR alters dopamine turnover and induces anxiety and depressive-like behaviors. These findings demonstrate a potential molecular link between central insulin resistance and behavioral disorders (Kleinridders et al., 2015). Furthermore, another study suggested that the somatic-vegetative symptoms of depression may worsen insulin resistance and increase diabetes risk, partly, by increasing body mass index (Khambaty et al., 2014). Interestingly, in a cross-sectional and prospective study in a community representative sample of 3140 older men free of diabetes, Ford et al. (2015) found that older men with clinically significant depressive symptoms were more likely to have higher markers of IR, and IR increased the risk of developing depression over 5 years later.

Depression is twice as common in people with stroke or diabetes as in the general population (Mitchell et al., 2017; Nouwen et al., 2010), and is associated with poor outcomes (Coleman et al., 2013; Gainotti et al., 2001). Post-stroke depression (PSD) worsened stroke-related outcomes in the form of greater functional disability and higher mortality (Cheng et al., 2014). It increases the cost of treatment and burden of care to families, making the prevention and management of PSD an important area of research. However, there have been no studies on IR in patients with PSD. The lack of data in this field provided the impetus for the study reported herein. Furthermore, the homeostasis model assessment (HOMA) is a widely used clinical and epidemiologic tool for

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indirect estimates of insulin sensitivity and insulin secretion. Thus, we hypothesize that HOMA-IR at admission is associated with prevalence of PSD later developed, and HOMA-IR might be a major risk factor for PSD. In this prospective, multicenter cohort study of 698 Chinese patients with acute ischemic stroke (AIS), we assess the value of HOMA-IR at admission to predict PSD later developed at 3 months follow-up.

2. Patients and methods

2.1. Study population

This prospective, multicenter cohort study was conducted at 3 Stroke Centers from 3 cities (Beijing, Weifang and Wuhan) in China. Patients were eligible for inclusion if they were admitted to the emergency department with a first-ever AIS defined according to the World Health Organization ICD-9 criteria (Hatano, 1976) and with symptom onset within 24 h. The number of stroke patients attended during the study period (From January 2015 through December 2016) determined the sample size. Patients with known acute infection, cardiogenic shock, malignancy, missing informed consent or blood samples, intracerebral hemorrhage, transient ischemic attack (TIA), a history of recent surgery or trauma during the preceding 3 months, renal insufficiency (creatinine > 1.5 mg/dl), died in the follow-up, as well as those with a history of valvular heart disease and heart failure were excluded. The patients used psychotropic drugs prior to stroke onset or had a history of psychiatric disorders were also excluded. The study was approved by the ethics committee of the Weifang medical University Hospital according to the principles of the Declaration of Helsinki. The patients or their relatives gave written informed consent prior to entering the study.

2.2. Clinical variables

At baseline, the following demographical and clinical data were taken: gender, age, BMI (Body Mass Index), smoking history (never, former, or current), alcohol consumption (g/week), history of conventional vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation and hyperlipoproteinemia) and prior or acute treatment were obtained. All patients received treatment according to current guidelines. Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS) score (Brott et al., 1989) by two neurologists (Qiu H and Li X). The NIHSS scores range from 0 to 42, with greater scores indicating increasing severity. Ischemic stroke subtype was classified by a consensus of 2 neurologists (Qiu H and Li X), with a third neurologist (Zeng X) adjudicating if needed, based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria (Adams et al., 1993). The clinical stroke syndrome was determined by applying the criteria of the Oxfordshire Community Stroke Project. A baseline brain computer tomography (CT) or magnetic resonance imaging (MRI) scan were performed in all patients within 24 h after admission. If MRI was performed(N = 402), using a double-blind interview methodology (Tu et al., 2017), the presence of diffusion-weighted imaging(DWI) lesions was assessed through the consensus of two experienced raters. The infarct volume was calculated using the following formula: 0.5 × a × b × c (where *a* is the maximal longitudinal diameter, *b* is the maximal transverse diameter perpendicular to *a* and *c* is the number of 10-mm slices containing infarct) (Sims et al., 2009). Functional outcome was also obtained according to the modified Rankin Scale (mRS) score at follow-up.

2.3. End points and depression assessment

The primary end-point was psychological evaluation on month 3 after admission by the trained psychologist (Qiu H and Zeng X). Participants completed the Beck Depression Inventory Fast Screen (BDI-FS) (Healey et al., 2008). The BDI-FS is a 7-item version of the standard Beck Depression Inventory intended for use in clinic populations with coexisting medical issues. Participants are asked to choose 1 statement for each item that best describes the way they have been feeling in the past 2 weeks. Each item is rated on a 4-point scale ranging from 0 to 3. Total scores are computed as the sum of the score for all 7 items, and range from 0 to 21. This scale has been validated in a series of studies of family practice and internal medicine patients, published in the BDI-FS manual. We considered BDI-FS scores as a linear scale and across 4 categories. The following recommended categories were considered: 0–4: not depressed; 5–8: at risk for mild depression; 9–12: at risk for moderate depression; 13–21: at risk for severe depression (Greenwood et al., 2015). Inter-rater reliability between different psychologist was examined in 50 patients and the kappa was 0.88. We have used the validated version for the Chinese population. Data concerning demographics, level of education, living situation, family history of psychiatric disorders, and drug treatment were also collected by interview. Those evaluation were conducted by neurologists/psychiatrists who were unaware of the type, size and location of the index stroke at the time of the investigation and throughout the diagnostic procedure.

2.4. Blood collection and laboratory test

Blood samples were collected via venipuncture in ethylenediaminetetraacetic acid (EDTA) BD Vacutainer® (New Jersey, USA) tubes at 7:00 am on the morning after the admission under fasting state and within 48 h of onset of stroke symptoms/signs (within 0–6 h [n = 137], 6–12 h [n = 169], 12–24 h [n = 201], and 24–48 h [n = 191] from the symptom onset). Blood samples were centrifuged at 1000 × *g* for 12 min and plasma was separated and stored at −80 °C until the time of assay. Biochemical measurements were done using standard laboratory methods. Insulin level was measured with a commercial enzyme-linked immunosorbent assay (ARCHITECT insulin assay; Abbott, Wiesbaden, Germany) and other biochemical parameters (triglyceride, low and high-density lipoprotein, homocysteine(HCY)), fasting blood glucose (FBG) and high-sensitivity C-reactive protein (Hs-CRP) were assessed using ROCHE COBASC311 (ROCHE, Basel, Switzerland). Determinations were performed in duplicate, and the mean value of both determinations was used. The mean intra-assay coefficients of variation were less than 10% in all cases. IR was quantified with the homeostatic model assessment index (HOMA-IR) following the formula described by Matthews et al.: HOMA-IR = fasting serum insulin (μU/mL) × fasting blood glucose (mmol/l)/22.5 (Matthews et al., 1985).

2.5. Statistical analysis

Results were expressed as percentages for categorical variables and as means (standard deviation, S.D.) or medians [interquartile range (IQR)] for the continuous variables, depending on the normal or non-normal distribution of data. Proportions were compared using the $\chi 2$ test, and student's *t*-test and analysis of variance (ANOVA) were employed for the normally distributed variables, while the Mann–Whitney *U*-test was employed for the asymmetrically distributed variables.

The influence of HOMA-IR on PSD was performed by binary logistic regression analysis, which allows adjustment for confounding factors (age, sex, BMI, NIHSS score, time from onset to stroke etiology, pre- or acute stroke treatment, family history of psychiatric disorders, widowhood and living with offspring, vascular risk factors and serum levels of Hs-CRP, HCY, HDL, LDL and triglycerides). Results were expressed as adjusted odds ratios (OR) with the corresponding 95% confidence interval (CI). For a more detailed exploration of the HOMA-IR and PSD outcome, we also used multivariate analysis models to estimate adjusted OR and 95% CIs of PSD for HOMA-IR quartiles (with lowest HOMA-IR quartile as reference). In addition, the relationship between patients in IR group (HOMA-IR Q4 vs. Q1-3) and PSD was also calculated.

Further, receiver operating characteristic curves (ROC) was used to