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Elevated bilirubin after acute ischemic stroke linked to the stroke severity

Yun Luo [a,b], Jingwei Li [a], Junfeng Zhang [b,*], Yun Xu [a]

[a] Department of Neurology, Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China
[b] School of Life Science, Nanjing University, Nanjing 210093, China

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ABSTRACT

Background: Our previous study demonstrated that the level of serum bilirubin after acute ischemic stroke (AIS) was correlated to the severity of stroke, also there has the evidence of hyperbilirubinemia prevalent in AIS. We aimed to identify the exact change of bilirubin in the early phase of AIS, and study if this kind of change linked to the severity of stroke.

Methods: Bilirubin and other biochemical indexes were measured in 608 AIS patients and 188 transient ischemic attack (TIA) patients which set as the control group. National Institutes of Health Stroke Scale (NIHSS) scores were assessed simultaneously with blood collection. First, the level of bilirubin and its distribution were compared between the AIS and control group. According to a cut-off point, we next analyzed the impacted factors of elevated bilirubin including the direct bilirubin (Dbil) and total bilirubin (Tbil), especially the correlation between elevated bilirubin and the severity of stroke. Finally, we compared the difference of concentration and percent of elevated bilirubin among the Oxford Community Stroke Project (OCSP) subtypes.

Results: The level of serum Dbil and Tbil was significantly higher in the AIS group than that in the TIA group. Different distribution was observed between the two groups, which manifested as the percent of low bilirubin level group was lower while high level group was higher in AIS than that in TIA, the p value were 0.043 and 0.078 in Dbil and Tbil, respectively. When the cut-off point of elevated bilirubin was selected as Dbil $\geq$ 6.84 μmol/L and Tbil $\geq$ 22.2 μmol/L, we found that both NIHSS score and relative severity of AIS were significantly associated with elevated bilirubin whenever in Dbil or Tbil, so did the OCSP subtypes. This trend was still maintained by multivariable logistic regression analysis adjust for relative influence factors. In regard of OCSP subtypes, the highest level of bilirubin was found in TACI, so did the highest rate of elevated bilirubin.

Conclusion: The serum levels of Dbil and Tbil were increased after AIS, which linked to the severity of stroke.

1. Introduction

Excessive oxidative stress induced the functional and structural damage of brain through the whole course of AIS, especially the early phase, which may play an important role in the pathophysiology of brain insult (Niizuma et al., 2009; Chen et al., 2010). As a protective reaction, to keep the balance of oxidative and antioxidative system, antioxidative agent should be stirred in the course of AIS because of its strong oxidative stress. It had been reported in a series of studies.

Bilirubin is an end product of heme metabolism and thought to be one of the strongest endogenous antioxidant substances in mammalian tissues (Stocker et al., 1987). Nowadays, more and more attentions were paid to its role of reducing the formation of carotid atherosclerotic plaque and occurrence of ischemic stroke (Ishizaka et al., 2001; Vitek et al., 2006; Kimm et al., 2009), however, little was known about its change and role in the early phase of AIS.

Despite Herishanu et al. (1971) found that higher percentage of hyperbilirubinemia was prevalent in the acute ischemic stroke, they just found this phenomenon and did not interpret it reasonably. Also, the exact change of bilirubin in the AIS was unclear. More severe stroke linked with higher level of oxidative stress, so did the antioxidant. Our previous study showed that serum bilirubin after acute ischemic stroke was associated with stroke severity

* Corresponding author.
E-mail addresses: jfzhang@nju.edu.cn (J. Zhang), xuyun20042001@yahoo.com.cn (Y. Xu).

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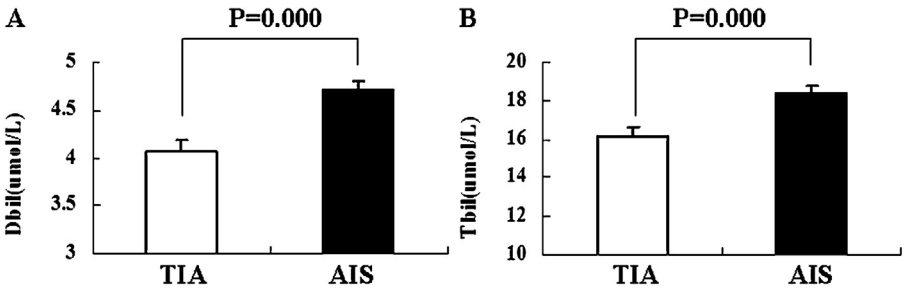

Fig. 1. Comparison of the Dbil and Tbil between TIA and AIS group.

(Luo et al., 2012). To illustrate its exact change and impacted factors, we assess and compare the serum level of bilirubin between TIA and AIS group, and observe the factors which will induce the upregulation of the bilirubin.

2. Subjects and methods

2.1. Patient and control selection

Data for this retrospective study were collected from all AIS patients within 7 days of symptom onset in Affiliated Drum Tower Hospital of Nanjing University Medical School from October 2008 to May 2012. The study was approved by our institutional committee. At admission, plain CT scan of the head was done to rule out cerebral hemorrhage and MRI was done to identify the new infarction. Exclusion criteria were: (1) patients who were found with pre-stroke impairment or infections or inflammatory diseases; (2) patients with established history of hepatic, cholecystic or renal disease and tumor. The controls were hospitalization patients with TIA selected in the same time period. The same exclusion criteria used in the AIS group was also applied to the control group.

2.2. Definition of vascular risk factors

Hypertension and diabetes mellitus (DM) were defined as participants with history of relative disease or new diagnosis according to the China hypertension and DM standard, while atrial fibrillation (AF) was defined as participants with history of AF or new diagnosis by electrocardiogram.

2.3. Clinical parameters

Stroke severity was assessed with the NIHSS score by two neurologists at admission, and NIHSS ≥ 8 was assigned to be a relative severe AIS. OCSP stroke subtype is a clinical classification used in population studies, which provided information on the clinical extent of brain damage, included total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), lacunar infarction (LACI), posterior circulation infarction (POCI), can also reflect the severity of AIS partly.

2.4. Blood collection and analysis

Venous blood was collected following overnight fasting for at least 12 h, and analyzed by a solid-phase chemiluminescent immunometric assay on Immulite 2000 with the manufacturer's reagents as directed to detect Dbil and Tbil. Also, blood glucose (BG), uric acid (UA), triglyceride (TG), cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured by the same way simultaneously.

2.5. Statistical analyses

Statistical analyses were performed with SPSS 10.0 software. The results are expressed as percentages for categorical variables (Pearson χ^2 test) and as mean $\pm$ SEM for the continuous variables (t-test) depending on their normal distribution. The level-risk relationship was expressed as an OR, with a corresponding 95% CI, through logistic regression. Level of significance for statistical purposes was stated at $p < 0.05$.

3. Results

3.1. Baseline characteristics and bilirubin levels in AIS patients and controls

608 patients with AIS were included in the trial, among them, 383 were male and 225 were female, whose age ranges from 15 to 92. 432 patients had hypertension, 201 patients had DM and 81 patients had AF coexistence with AIS. While the control group contained the 188 TIA patients, with age- and sex-comparable to the AIS group, and the incidence of hypertension and DM and AF was also similar.

The serum levels of Dbil and Tbil were significantly higher in the AIS group than that in the TIA group, as shown in Fig. 1A (4.070 vs 4.702 μmol/L, $p < 0.001$) and B (16.147 vs 18.329 μmol/L, $p < 0.001$).

3.2. High level of serum bilirubin was observed in the AIS

Both Dbil and Tbil concentrations were grouped into 4 levels: Dbil: 0–3.42, 3.43–5.13, 5.14–6.84, ≥6.84 μmol/L; Tbil: 0–10.2, 10.3–15.3, 15.4–22.1, ≥22.2 μmol/L (1 mg/dL = 17.1 μmol/L, multiply by 17.1). We analyzed the difference of distribution of Dbil and Tbil between the TIA and AIS group, and found that, the percent of low Dbil level group (0–3.42) was lower in AIS than that in TIA (31% vs 41%), while high level group (≥6.84) was higher in AIS than

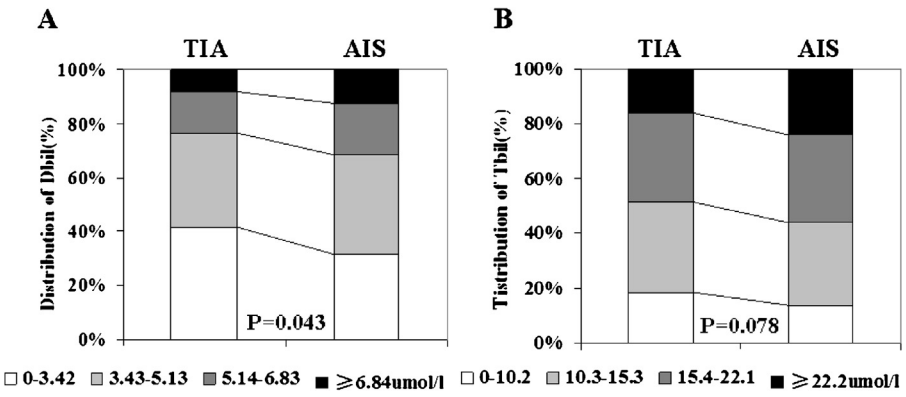

Fig. 2. Distribution of Dbil and Tbil levels in the analyzed population.