The longitudinal changes of serum JKAP and IL-17A, and their linkage with anxiety, depression, and cognitive impairment in acute ischemic stroke patients

Chaohui Wang1 | Huiyong Huo1 | Juntao Li1 | Wenchao Zhang1 | Chao Liu1 | Bei Jin2 | Huijuan Wang1 | Ping Zhao1

1Second Department of Neurology, HanDan Central Hospital, Handan, China
2First Department of Pediatric Surgery, HanDan Central Hospital, Handan, China

Abstract
Background: Our previous study discovers that Jun N-terminal kinase pathway-associated phosphatase (JKAP) is dysregulated and negatively links with the disease severity in acute ischemic stroke (AIS) patients. This study intended to further evaluate the linkage of JKAP and interleukin (IL)-17A with anxiety, depression, and cognitive impairment in AIS patients.

Methods: Serum JKAP and IL-17A levels in 120 AIS patients at admission, 1st (D1), 3rd (D3), 7th (D7) day after admission, and from 20 controls, were detected by ELISA. Hospital Anxiety and Depression Scale (HADS) and Mini-Mental State Examination (MMSE) were assessed in AIS patients at discharge.

Results: JKAP (p<0.001) was reduced, but IL-17A (p<0.001) was increased in AIS patients versus controls, and negatively correlated with each other in AIS patients (p = 0.014). In AIS patients, JKAP was reduced from baseline to D1 and then increased to D7 (p<0.001), while IL-17A exhibited an opposite trend (p<0.001). Notably, JKAP at D3 was negatively linked with HADS-anxiety score (p = 0.044), then decreased JKAP at D3 (p = 0.017) and D7 (p = 0.037) related to increased anxiety occurrence. However, JKAP was not linked to HADS-depression score or depression occurrence. Besides, JKAP at multiple time points were positively associated with MMSE score (all p<0.05); decreased JKAP at D3 (p = 0.017) and D7 (p = 0.026) related to raised cognitive impairment occurrence.

Conclusion: JKAP initially decreases then shows an increasing trend after disease onset, and its decrement relates to elevated IL-17A, anxiety and cognitive impairment in AIS patients.

Keywords: acute ischemic stroke, anxiety and depression, cognitive impairment, interleukin-17A, Jun N-terminal kinase pathway-associated phosphatase.
1 | INTRODUCTION

Acute ischemic stroke (AIS) is the most prevalent type of stroke, which is partly attributed to the abrupt obstruction of a blood vessel by a thrombus, resulting in diminished oxygen supply to the brain, and further leading to loss of neurologic function. In China, among 29 million cases of stroke, 23 million cases are AIS, and 2.2 million people die from AIS per year; besides, smoking, a high diet of sodium, high systolic blood pressure, and exposure to environmental particulate matter pollution are four major risk factors for AIS. At present, the treatment options for AIS patients include antiplatelet therapy, thrombolysis, anticoagulants, thrombectomy, etc., which have achieved certain advancements in AIS patients. Nevertheless, there is still a large portion of AIS patients suffering from post-stroke complications, such as paralysis, partial loss of hearing or vision, incoherent speech, etc. Worse still, post-stroke anxiety, depression, and cognitive impairment also frequently occur in AIS patients due to the impaired neurological function of the brain, which further contributes to the poor prognosis. Therefore, exploring new biomarkers that link with anxiety, depression, and cognitive impairment would be meaningful for improving the psychological health of AIS patients.

Jun N-terminal kinase (JNK) pathway-associated phosphatase (JKAP), as a key JNK regulator, inactivates T-cell receptor (TCR) signaling to involve in T-cell mediated immunity, and suppresses Lck to reduce the secretion of interleukin (IL)-17A, thereby participating in the pathology and progression of neurological diseases. Besides, a few studies also report the linkage of JKAP and IL-17A with mental health in inflammation-mediated and neurological disease patients. For instance, JKAP is reversely linked with cognitive impairment progression in Alzheimer's disease patients. In terms of IL-17A, it is positively linked with anxiety, depression, and cognitive impairment in AIS patients. Importantly, our recently published study discovers that JKAP is reduced, and negatively related to the National Institutes of Health Stroke Scale (NIHSS) score in AIS patients; however, the intercorrelation between JKAP and IL-17A, and their clinical role in estimating psychological health in AIS patients should be further explored.

Accordingly, this study aimed to estimate the longitudinal changes of JKAP and IL-17A, as well as their linkage with anxiety, depression, and cognitive impairment in AIS patients.

2 | METHODS

2.1 | Subjects

A total of 120 first-episode AIS patients who were treated in our hospital from March 2020 to September 2021 were consecutively included. The inclusion criteria contained: (1) diagnosed as first-episode AIS per Guidelines from American Stroke Association; (2) aged more than 18 years; (3) with no intracranial hemorrhage; (4) willing to comply with the study protocol. Pregnant females, breastfeeding females, or patients with malignancies were ineligible for inclusion. Besides, the study also enrolled 20 subjects who had at least two risk factors for stroke (including smoke, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, shortage of exercise, family history, etc.) as controls. The study was approved by the Ethics Committee. Informed consent was signed by each patient or the family.

2.2 | Collection of clinical data and samples

Clinical characteristics were, respectively, gained from AIS patients and controls after inclusion. Serum was obtained from AIS patients at admission, the 1st day after admission (D1), the 3rd day after admission (D3), and the 7th day after admission (D7), as well as from controls after enrollment. Then, JKAP level and IL-17A level were detected by Enzyme-Linked Immunosorbent Assay (ELISA) using commercial Human ELISA kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.) per the instructions.

2.3 | Assessment of cognitive impairment, anxiety, and depression

For AIS patients, Mini-Mental State Examination (MMSE), Hospital Anxiety and Depression Scale (HADS) for anxiety (HADS-A), and HADS for depression (HADS-D) were, respectively, scored on the day of discharge for cognitive impairment, anxiety, and depression assessment. Patients who died during hospitalization were excluded from the assessment and analysis. The HADS assessment was not performed for patients with MMSE < 20 at discharge. For controls, cognitive impairment, anxiety, and depression were also evaluated using MMSE, HADS-A, and HADS-D.

2.4 | Statistical analysis

Analysis was completed by SPSS v.22.0 (IBM Corp.). Graphing was realized by GraphPad Prism v.7.01 (GraphPad Software Inc.). Comparative analyses were carried out by Wilcoxon rank sum test, Chi-square test, Fisher’s exact test, or Student’s t test. The receiver-operating characteristic (ROC) curve analyses were used for distinguishing different subjects. Association analyses were accomplished by Spearman’s rank correlation test. Changes over time were assessed using Friedman’s test or Wilcoxon signed-rank test. p < 0.05 was considered significant.

3 | RESULTS

3.1 | Study flow

Totally, 120 AIS patients and 20 controls were consecutively enrolled. In AIS patients, peripheral blood (PB) samples were collected at baseline, D1, D3, and D7 to detect JKAP and IL-17A levels;
Meanwhile, the MMSE score and HADS score were evaluated at discharge. In controls, PB samples were collected at enrollment to detect JKAP and IL-17A levels; at the same time, the MMSE score and HADS score were also assessed at enrollment. All participants with available data were included in the analysis (Figure 1).

3.2 | Clinical characteristics in AIS patients and controls

The mean age was 66.8 ± 9.0 years in AIS patients and 67.3 ± 7.1 years in controls. Meanwhile, there were 39 (32.5%) females and 81 (67.5%) males in AIS patients, as well as 8 (40.0%) females and 12 (60.0%) males in controls. Comparison analysis showed that the demographical features and comorbidities did not differ between AIS patients and controls (all \(p > 0.05\)). Besides, the MMSE score (\(p = 0.003\)) was reduced, but the HADS-A score (\(p < 0.001\)), HADS-D score (\(p < 0.001\)), anxiety rate (\(p = 0.010\)), and depression rate (\(p = 0.022\)) were increased in AIS patients in contrast to controls. However, the cognitive impairment rate was not different between AIS patients and controls (\(p = 0.163\)). In AIS patients, the median (interquartile range [IQR]) value of duration since symptom to admission was 4.0 (3.0–6.0) h; the mean NIHSS score was 9.2 ± 4.6. Meanwhile, 97 (80.8%) and 23 (19.2%) patients received thrombolysis and mechanical embolectomy, separately. Notably, the median (IQR) duration from symptom to admission was 4.0 (3.0–6.0) h (Table 1).

3.3 | JKAP and IL-17A expressions, as well as their intercorrelation in AIS patients and controls

JKAP was reduced in AIS patients (median [IQR]: 42.3 (34.2–57.4) pg/ml in contrast to controls (median [IQR]: 81.1 (60.8–119.5) pg/ml) (\(p < 0.001\)) (Figure 2A); meanwhile, JKAP had a good capacity for discriminating AIS patients from controls (area under the curve (AUC): 0.856, 95% confidence interval (CI): 0.786–0.926) (Figure 2B). In contrast, IL-17A was raised in AIS patients (median [IQR]: 72.5 (56.5–121.3) pg/ml) compared to controls (median [IQR]: 40.3 (33.4–62.6) pg/ml) (\(p < 0.001\)) (Figure 2C); besides, IL-17A showed a good ability for distinguishing AIS patients from controls (AUC: 0.805, 95% CI: 0.695–0.914) (Figure 2D). Moreover, JKAP was inversely linked to IL-17A in AIS patients (\(r = -0.224\), \(p = 0.014\)) (Figure 2E), but not in controls (\(p = 0.145\)) (Figure 2F).

3.4 | Longitudinal changes of JKAP and IL-17A in AIS patients

JKAP showed a declining trend from baseline to D1, then it gradually increased from D1 to D7 in AIS patients (\(p < 0.001\)). Further comparison analysis found that JKAP at D1 (\(p < 0.001\)) was decreased compared to JKAP at baseline; meanwhile, JKAP at D3 (\(p < 0.001\)) was increased compared to JKAP at baseline; however, JKAP at D7 (\(p = 0.111\)) did not differ compared to JKAP at baseline (Figure 3A). Oppositely, IL-17A exhibited an increasing trend from baseline to D1, then it gradually reduced from D1 to D7 in AIS patients (\(p < 0.001\)). Further comparison analysis discovered that IL-17A at D1 (\(p < 0.001\)) was increased in contrast with IL-17A at baseline; while IL-17A at D3 (\(p < 0.001\)) and D7 (\(p = 0.001\)) were decreased compared with IL-17A at baseline (Figure 3B).

3.5 | Correlation of JKAP and IL-17A at different time points with anxiety and depression in AIS patients

In AIS patients, JKAP at D3 was negatively linked to the HADS-A score (\(r = -0.193\), \(p = 0.044\)); while JKAP at baseline (\(p = 0.353\)), D1 (\(p = 0.076\)), and D7 (\(p = 0.104\)) were not linked to the HADS-A score. Besides, no linkage was observed between JKAP at any time point and the HADS-D score (all \(p > 0.05\)) (Table 2). Further comparison analyses observed that JKAP at D3 (\(p = 0.017\)) and D7 (\(p = 0.037\)) were reduced in AIS patients with anxiety compared to those without anxiety; whereas, JKAP at baseline (\(p = 0.179\)) and D1 (\(p = 0.082\)) did not differ between them. Meanwhile, JKAP at D7 was decreased in AIS patients with depression in contrast to those without depression (\(p = 0.037\)); however, JKAP at baseline (\(p = 0.248\)), D1 (\(p = 0.069\)), and D3 (\(p = 0.054\)) were not different between them (Table 3).

In the aspect of IL-17A, its level at D1 (\(r = 0.196\), \(p = 0.032\)), D3 (\(r = 0.194\), \(p = 0.043\)), and D7 (\(r = 0.206\), \(p = 0.036\)), but not at baseline (\(p = 0.073\)), were positively linked to the HADS-A score. Additionally, IL-17A at D1 (\(r = 0.215\), \(p = 0.019\)), D3 (\(r = 0.241\), \(p = 0.012\)), and D7 (\(r = 0.251\), \(p = 0.010\)) were also positively related to the HADS-D score; however, no linkage was discovered between IL-17A at baseline and HADS-D score (\(p = 0.126\)) (Table 2). In addition, IL-17A at D1 (\(p = 0.034\)), D3 (\(p = 0.039\)), and D7 (\(p = 0.021\)) were increased in AIS patients with anxiety in contrast with those
without anxiety; nevertheless, IL-17A at baseline did not differ between them ($p = 0.172$). Moreover, IL-17A at baseline ($p = 0.386$), D1 ($p = 0.242$), D3 ($p = 0.228$), and D7 ($p = 0.053$) did not differ between AIS patients with and without depression (Table 3).

3.6 Correlation of JKAP and IL-17A at different time points with cognitive function in AIS patients

JKAP at baseline ($r = 0.213$, $p = 0.020$) (Figure 4A), D1 ($r = 0.237$, $p = 0.009$) (Figure 4B), D3 ($r = 0.342$, $p < 0.001$) (Figure 4C), and D7 ($r = 0.306$, $p = 0.002$) (Figure 4D) were all positively linked with MMSE score in AIS patients. Besides, IL-17A at baseline ($r = -0.217$, $p = 0.017$) (Figure 4E), D1 ($r = -0.350$, $p < 0.001$) (Figure 4F), D3 ($r = -0.346$, $p < 0.001$) (Figure 4G), and D7 ($r = -0.442$, $p < 0.001$) (Figure 4H) were inversely linked to MMSE score in AIS patients.

Further comparison analysis found that JKAP at baseline ($p = 0.123$) (Figure 5A) and D1 ($p = 0.063$) (Figure 5B) did not differ between AIS patients with and without cognitive impairment; while JKAP at D3 ($p = 0.017$) (Figure 5C) and D7 ($p = 0.026$) (Figure 5D) were reduced in patients with cognitive impairment in contrast to those without cognitive impairment. Additionally, IL-17A at baseline ($p = 0.017$) (Figure 5E), D1 ($p = 0.003$) (Figure 5F), D3 ($p = 0.006$) (Figure 5G), and D7 ($p < 0.001$) (Figure 5H) were all raised in AIS patients with cognitive impairment by comparison to those without cognitive impairment. Besides, it was also found that the absolute values (D7-baseline) of JKAP ($p = 0.396$) (Figure 6A) and IL-17A ($p = 0.134$) (Figure 6B) were not different between patients with cognitive impairment and those without cognitive impairment.
DISCUSSION

Our recently published study has revealed the dysregulation of JKAP in AIS patients, and this finding is confirmed by the current study\textsuperscript{17}; however, the longitudinal change of JKAP and IL-17A in AIS patients is still unclear. Therefore, the present study further explored this aspect. It was discovered that JKAP from baseline to D1 was reduced, then it showed an upward trend from D1 to D7 in AIS patients; while IL-17A exhibited an opposite trend. The possible explanation would be that: reduced JKAP could aggravate inflammation and immunity by activating Lck to regulate the TCR signaling; thus, JKAP could reflect inflammation to a certain extent\textsuperscript{14}; while the inflammation of AIS patients would be anabatic at the initial time of treatment, then with the benefits from the treatment, the inflammation might be gradually attenuated. As a result, JKAP was decreased from baseline to D1, and then it was gradually...
increased from D1 to D7. In terms of IL-17A, it showed an opposite trend to JKAP. The possible reason might be that: (1) IL-17A is a well-known proinflammatory cytokine, therefore, changed along with the inflammation during D7; (2) reduced JKAP could boost T helper (Th) 17 cells to secret IL-17A, then our recently published study also reveals that JKAP negatively relates to IL-17A in AIS patients.13,14,17 Therefore, IL-17A exhibited an opposite trend to JKAP.

Notably, the clinical role of JKAP is discussed in rheumatic diseases, such as ankylosing spondylitis and rheumatoid arthritis.23–25 These studies reveal that JKAP is negatively associated with disease activity in both ankylosing spondylitis and rheumatoid arthritis patients. Meanwhile, JKAP is gradually increased after treatment in rheumatoid arthritis patients26; besides, JKAP is also negatively related to IL-17A in ankylosing spondylitis patients, which is in line with the current study.23

Post-stroke anxiety and depression are prevalent in AIS patients26; however, the linkage of JKAP and IL-17A at multiple time points after disease onset with these psychological issues in AIS patients is unclear. Therefore, the current study further evaluated this aspect and discovered the following findings. First of all, JKAP was inversely related to the HADS-A score and anxiety occurrence; however, almost no linkage of JKAP with HADS-D score and depression occurrence was observed in AIS patients. The potential arguments would be that: (1) decreased JKAP could facilitate Th cells differentiation, leading to the excessive microglia activation and the recruitment of other immune cells, which could further contribute to the occurrence of anxiety;13,14,27 (2) reduced JKAP might also activate the JNK pathway to induce anxiety.28 Therefore, JKAP was reversely linked to anxiety in AIS patients. In terms of IL-17A, it was positively related to the HADS-A score and anxiety occurrence, as well as the HADS-D score in AIS patients. The possible reason would be that: IL-17A production might enhance the neuronal activation in the medial prefrontal cortex, or activate the kynurenine pathway to reduce serotonin levels, thereby inducing anxiety and depression in AIS patients.29,30

In addition, this study also evaluated the correlation of JKAP and IL-17A at multiple time points after disease onset with cognitive impairment in AIS patients. It was observed that JKAP was positively related to MMSE score, and inversely linked with the occurrence of cognitive impairment. The possible explanation would be that: reduced JKAP could facilitate the differentiation of Th cells, which contributed to the chronic neuroinflammation, and further led to cognitive impairment in AIS patients.14,27 However, a detailed mechanism of the regulatory role of JKAP in cognitive impairment in AIS patients was required. Concerning IL-17A, it was inversely linked to MMSE score and positively correlated with cognitive impairment occurrence in AIS patients. The potential arguments would be that: (1) IL-17A could regulate microglial activation to facilitate

| TABLE 2 | Correlation of JKAP level and IL-17A level with HADS score among AIS patients |
| Items | JKAP level (pg/ml) | HADS-A score | | | HADS-D score | | | |
| | | r value | p value | | | r value | p value | |
| At baseline | 0.086 | 0.353 | | | −0.050 | 0.585 | |
| At D1 | −0.163 | 0.076 | | | −0.107 | 0.246 | |
| At D3 | −0.193 | 0.044 | | | −0.165 | 0.087 | |
| At D7 | −0.160 | 0.104 | | | −0.137 | 0.165 | |
| IL-17A level (pg/ml) | | | | | | | |
| At baseline | 0.164 | 0.073 | | | 0.140 | 0.126 | |
| At D1 | 0.196 | 0.032 | | | 0.215 | 0.019 | |
| At D3 | 0.194 | 0.043 | | | 0.241 | 0.012 | |
| At D7 | 0.206 | 0.036 | | | 0.251 | 0.010 | |

Abbreviations: AIS, acute ischemic stroke; D1, the 1st day after admission; D3, the 3rd day after admission; D7, the 7th day after admission; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale for depression; HADS-D, Hospital Anxiety and Depression Scale for depression; IL-17A, interleukin-17A; JKAP, Jun N-terminal kinase pathway-associated phosphatase.

| TABLE 3 | Correlation of JKAP level and IL-17A level with anxiety and depression among AIS patients |
| Items | Anxiety | | | Depression | |
| | | No | Yes | Z value | p Value | No | Yes | Z value | p Value | |
| JKAP level (pg/ml) | | | | | | | | | |
| At baseline, median (IQR) | 44.3 (36.1–58.9) | 39.6 (29.0–57.1) | | −1.344 | 0.179 | 44.3 (36.1–56.9) | 39.5 (28.2–58.8) | | −1.155 | 0.248 |
| At D1, median (IQR) | 34.5 (27.6–47.3) | 30.9 (22.7–45.2) | | −1.737 | 0.082 | 34.5 (27.7–47.6) | 30.8 (22.0–43.2) | | −1.819 | 0.069 |
| At D3, median (IQR) | 39.6 (29.5–56.6) | 30.9 (22.2–48.8) | | −2.381 | 0.017 | 39.5 (28.6–55.1) | 30.9 (21.6–52.2) | | −1.930 | 0.054 |
| At D7, median (IQR) | 45.8 (36.1–63.7) | 39.4 (30.0–56.3) | | −2.084 | 0.037 | 45.8 (35.6–63.2) | 38.9 (29.1–57.0) | | −2.086 | 0.037 |
| IL-17A level (pg/ml) | | | | | | | |
| At baseline, median (IQR) | 69.5 (56.5–100.0) | 84.9 (56.8–134.1) | | −1.367 | 0.172 | 72.4 (56.6–106.0) | 74.3 (56.3–133.5) | | −0.866 | 0.386 |
| At D1, median (IQR) | 91.2 (70.0–129.6) | 104.3 (83.2–164.7) | | −2.121 | 0.034 | 92.8 (72.3–138.6) | 101.2 (79.7–162.9) | | −1.169 | 0.242 |
| At D3, median (IQR) | 82.5 (55.4–141.6) | 110.2 (69.7–158.8) | | −2.062 | 0.039 | 85.1 (56.4–144.1) | 100.7 (67.8–155.6) | | −1.204 | 0.228 |
| At D7, median (IQR) | 57.4 (38.5–95.5) | 77.8 (51.5–122.4) | | −2.309 | 0.021 | 58.1 (40.7–100.4) | 76.1 (50.7–127.3) | | −1.937 | 0.053 |

Abbreviations: AIS, acute ischemic stroke; D1, the 1st day after admission; D3, the 3rd day after admission; D7, the 7th day after admission; IL-17A, interleukin-17A; JKAP, Jun N-terminal kinase pathway-associated phosphatase.
FIGURE 4  Linkage of JKAP and IL-17A at baseline, D1, D3, and D7 with MMSE score. JKAP at baseline (A), D1 (B), D3 (C), and D7 (D) was positively linked to MMSE score; IL-17A at baseline (E), D1 (F), D3 (G), and D7 (H) was inversely linked with MMSE score in AIS patients.

FIGURE 5  Comparison of JKAP and IL-17A at baseline, D1, D3, and D7 between patients with and without cognitive impairment. JKAP at baseline (A) and D1 (B) was not different between AIS patients with and without cognitive impairment; while JKAP at D3 (C) and D7 (D) was reduced in patients with cognitive impairment in contrast to those without cognitive impairment. IL-17A at baseline (E), D1 (F), D3 (G), and D7 (H) was increased in patients with cognitive impairment by contrast to those without cognitive impairment.

FIGURE 6  Changes (D7-baseline) of JKAP and IL-17A in patients with and without cognitive impairment. The absolute value (D7-baseline) of JKAP (A) and IL-17A (B) were not different between patients with cognitive impairment and those without cognitive impairment.
neuronal apoptosis, thereby inducing cognitive impairment\(^{21,22}\); (2) increased IL-17A could contribute to the cognitive deficits after ischemic stroke\(^{32}\); therefore, IL-17A was negatively linked with MMSE score, but positively related to cognitive impairment occurrence in AIS patients.

Notably, this study also estimated the prevalence of these mental and cognitive issues in AIS patients. It was discovered that the incidence of anxiety, depression, and cognitive impairment were 33.3%, 29.2%, and 25.0%, respectively, which was partly in line with a previous study (anxiety: 39.2%; depression: 31.2%; cognitive impairment: 43.2%).\(^{21}\) This finding indicated that anxiety, depression, and cognitive impairment were critical issues in AIS patients.

Several limitations should be noticed in this study: (1) this study did not focus on hemorrhage stroke patients; thus, the value of IL-17A and JKAP for anxiety, depression, and cognitive impairment in these patients needed to be further explored; (2) the detailed mechanism of JKAP and IL-17A involved in anxiety, depression, and cognitive impairment was not explored; (3) the HADS score was self-assessed; therefore, assessment bias might exist; (4) the long term changes of JKAP and IL-17A in AIS patients were not investigated in this study, which could be a direction for subsequent studies; (5) this study did not detect JKAP in plasma, and this could be a direction for further studies; (6) this study only applied HADS to estimate anxiety and depression, which might induce bias in the evaluation.

In summary, JKAP is initially reduced and then shows an increasing trend after AIS onset, its decrement links with elevated IL-17A, anxiety, and cognitive impairment in AIS patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Chaohui Wang  https://orcid.org/0000-0003-2106-1673
Ping Zhao  https://orcid.org/0000-0001-7219-2724

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