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CASE REPORT

Long Term Application of Artemether Improved Language and Cognitive Deficit of Chronic Ischemic Stroke Patient: A Case Report

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Abstract

Stroke is the first cause of death and disability among adults with limited treatment approaches. According to the Wolfe's survey, the five-year recurrence risk of ischemic stroke ranges from 15% to 40%. Given the rapidly growing number of ischemic stroke patients, it is urgent to develop more effective therapies for this disease. Artemether, the first line anti-malarial drugs, used in clinic for decades. It is safe, economic and concentrated in the brain after application. Our recent finding of the neuroprotective effect of artemether suggested its potential application in brain disorder including stroke patients, but no any information is available about its application in stroke in clinic at present. We report here, at the first time, a case of a cerebral ischemic stroke patient with lacunar infarction, successfully treated with artemether. A 78-year-old right-handed man presented with progressive cognitive decline, memory loss, motor paralysis and dysphagia, resulting from an ischemic cerebral stroke several years ago (year 2008). In 2011 the patient presented a score of 16 points in the National Institute of Health Stroke Scale (NISHSS) and over the years, his neurological deficits aggravated (NISHSS 32, February

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2018). Chronic ischemic stroke was diagnosed based on his clinical symptoms, Magnetic Resonance Imaging (MRI) and Transcranial Doppler (TCD) results. In July 2018, the patient was treated with a daily dose of artemether 80 mg for three months, after this, he was being able to speak some words, and then a maintenance dose of 20 mg/day was given to this patient. In October 2018, he presents a score of 18 in the NIHSS and being able to speak a whole sentence clearly, to talk with others and to walk slowly supported by the arm. Moreover, MRI showed a slightly improvement of IS and G showed CT follow-up without occlusion of trunk artery. This case indicates that artemether may have a therapeutic potential in chronic ischemic stroke patient.

Introduction

Stroke is one of the most serious and life-threatening conditions affecting a large number of patients all over the world. Currently, acute ischemic stroke is improved with the help of recombinant tissue plasminogen activator, antiplatelet and endovascular treatments [1-3]. However, there are still no clues of how to approach chronic ischemic stroke. The current stroke prevalence in China (1115 per 100,000 population) is among the highest in low- and middle-income countries. A recent survey indicated that there are at least 3.458 million new stroke patients and more than 1.61 million patients die from stroke every year in China. Indeed, China's stroke burden is among the most severe worldwide [4].

Artemisinin (ART) is a traditional Chinese medicine that has been used as a first-line anti-malaria drug for decades. It has been reported to possess neuroprotective properties towards H_2O_2, β-amyloid, SNP induced injury [5-7]. Artemether is an artemisinin derivative with a higher anti-malarial activity (The structural formula of artemether is shown in figure 1). Moreover, artemether can easily pass through the blood-brain barrier and it is used more frequently in the clinic, these shows that artemether has a potential protective effect in ischemic stroke. Given its medical and social importance, we believe it is necessary to explore the therapeutic potential of artemether in the recovery and symptom alleviation of elderly patients with chronic ischemic stroke.

According to our results, after a cerebral ischemic stroke patient was treated with a daily dose of artemether 80 mg for three months and then a maintenance dose of 20 mg/day, he presents a score of 18 in the NIHSS (before a score of 32 in the NIHSS) and being able to speak a whole sentence clearly, to talk with others and to walk slowly supported by the arm. Moreover, MRI showed a slightly improvement of IS and G showed CT follow-up without occlusion of trunk artery. These results provide evidences that artemether may have a therapeutic potential in chronic ischemic stroke patent.

Case report

3. A 78-year-old male patient previously diagnosed with Chronic Ischemic Stroke (IS) in 2008, presented increasing dizziness and unsteady gait. His first cranial MRI results were lost. Since 2011 the patient had been suffering from aggressive mental retardation, memory loss, anomia, motor paralysis and dysphagia and presents a score of 16 in the NIHSS. Subsequent cranial MRI revealed abnormal hypointense T1 and hyperintense T2 signals in the bilateral centrum ovale, corona radiata, bilateral ventricle

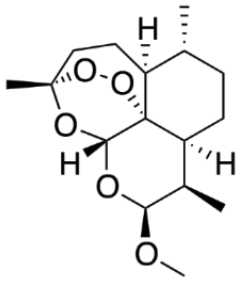

Figure 1 Chemical structure of Artemether.

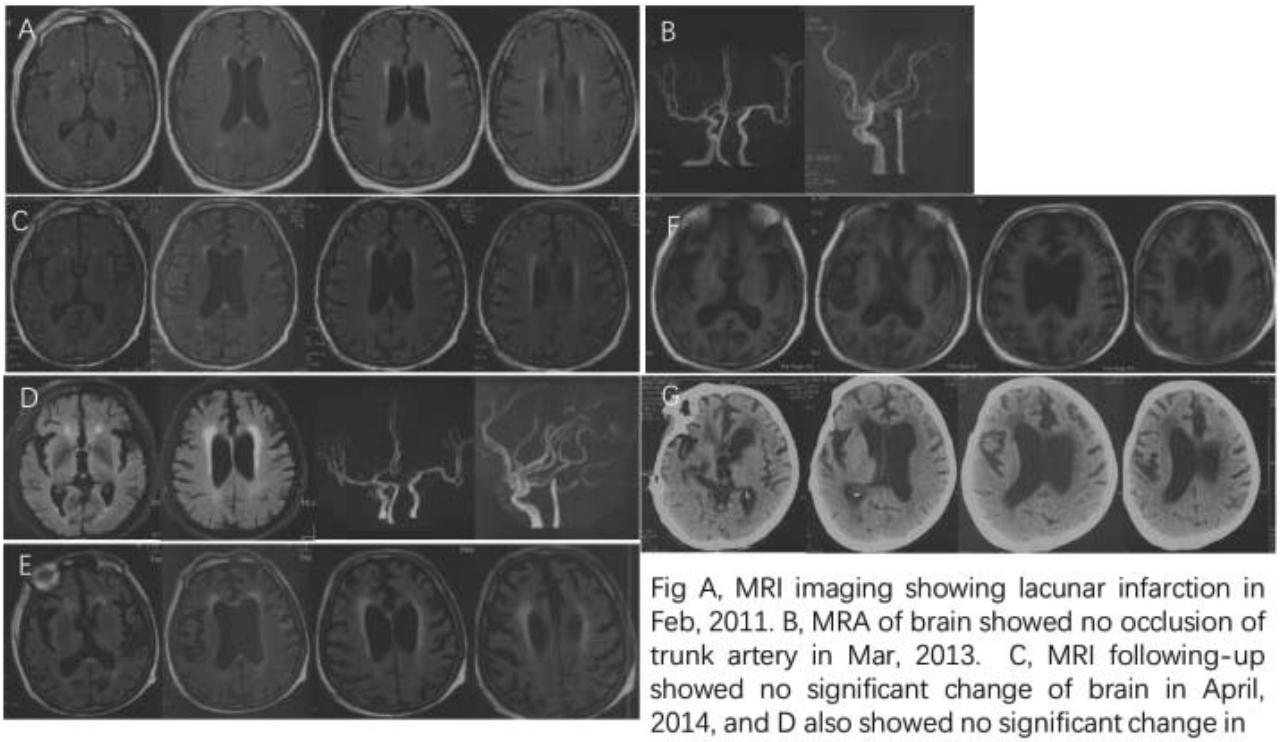

Figure 2 Serial neuroimaging findings during follow-up.
A: MRI showed lacunar infarction in Feb, 2011.
B: MRA of the brain showed no occlusion of trunk artery in Mar, 2013.
C: Follow-up MRI showed no significant changes in the brain in April, 2014
D: D also showed no significant change in MRI and MRA of brain in April, 2014.
E: MRI showed brain atrophy and hydrocephaly without increase of infarction volume in Sep, 2017.
F: MRI showed a slightly improvement of IS and G showed CT follow-up without occlusion of trunk artery.

and basal ganglia area of the cerebral hemisphere (Figure 2A). The neurological deficits didn't improve after treatment with several Chinese traditional anti-IS therapies, such as danhong and shuxuening injections. In fact, the symptoms exacerbated and in March 2013 the patient scored 25 points in the NIHSS. Genetic analysis was also performed for Triplet Repeat Disorders (TRDs), including spinocerebellar ataxia (SCA type 1, 2, 3, 6, 7, 8 and 17), dentatorubral-pallidoluysian atrophy (DRPLA), Huntington's disease (HD-1/IT15, HD-2/junctonphilin-3), spinal-bulbar muscular atrophy (SBMA), and Friedreich's ataxia (FRDA). However, the results from the genetic screening revealed that TRDs didn't affect the patient. Then, a new MRI was taken in April 2014 (Figure 2 C,D) and, from May 2014, the patient began to have more difficulties in walking and speaking, also presenting dementia signals (NIHSS 26). From February 2018, the symptoms aggravated, and the patient could no longer speak, walk or recognize anything, including the hints for defecation (NIHSS 32). After attempting treatment with amantadine hydrochloride, the neurological deficits still didn't improve. The son of the patient found Zheng's report about the protective effect of artemisinin [5,8,9]. He decided to give his father artemether treatment based on the finding of Zheng's papers. On July 2018, the patient was treated with artemether 80 mg/day. After one month of treatment, the patient

started being able to recognize his friends, to talk slowly and to walk supported by the arm (NIHSS 26). Moreover, MRI showed a slightly improvement of IS and G showed CT follow-up without occlusion of trunk artery (Figure 2F). Unfortunately, after 44 days of treatment, the patient also started to recite some ambiguous sentences and to kick indiscriminately. Hence, the patient stopped the artemether treatment at the 49th day and the ambiguous sentences and indiscriminately kicking gradually started disappearing. After some discussion, the doctors adjusted the artemether dosage to 20 mg/day. From October 2018, the patient started receiving a maintenance dose of 20 mg/day of artemether, and was again able to speak clearly, to talk with others and to walk slowly with support (NIHSS 18). In these years, the MRI analysis showed multiple lacunar infarctions in the cerebral and cerebellar hemispheres, and several TCD results showed many atherosclerotic plaques in the bilateral carotid artery, vertebral artery and even in the distal posterior cerebral artery. After artemether treatment, a slightly improvement of IS and G showed CT follow-up without occlusion of trunk arter

Discussion

Ischemic stroke has a high prevalence and constitutes the leading cause of death and disability in urban and rural areas of China. Approved drugs, such as aspirin or clopidogrel, have many limitations regarding the prevention or treatment of recurrent stroke after TIA or minor stroke in a long-term duration, including hemorrhagic stroke [10]. Moreover, the available treatments for chronic ischemic stroke are still very limited. Hence, it is urgent to develop of novel and more effective therapies against ischemic stroke.

In this study, we found that after a cerebral ischemic stroke patient was treated with a daily dose of artemether 80 mg for three months and then a maintenance dose of 20 mg/day, he presents an improvement of the score in the NIHSS (before a score of 32 in the NIHSS, after is 18). Moreover, the patient was being able to speak a whole sentence clearly, to talk with others and to walk slowly supported by the arm. MRI showed a slightly improvement of IS and G showed CT follow-up without occlusion of trunk artery. All these together, these evidences support the potential of artemisinin and its derivative artemether as a neuroprotective drug for the treatment of chronic ischemic stroke.

Artemisinin and its derivatives, including artemether, artesunate and dihydroartemisnin ect. These compounds can penetrate the blood brain barrier and are well-known as anti-malaria botanical drugs [11]. Importantly, the therapeutic effect of the artemisinin derivative artemether against cancer, human schistosomiasis [12], malnutrition [13], hepatonephritis [14], Alzheimer's disease [5] and many other medical conditions has been reported. Furthermore, Zheng, et al. [15] firstly found that artemisinin and its derivatives confer a neuroprotective effect through the activation of extracellular regulated protein kinases pathway, and revealed that artemisinin and its derivatives may be useful to the development of novel therapeutic concepts for brain disorders treatment [15-18]. In our study, the patient of this case report received a daily dose of 80 mg of artemether for 44 days. As a result, the patient's NIHSS scores decreased from 32 to 26. Unfortunately, the patient also started to recite some ambiguous sentences and to kick indiscriminately. This may due to the suspicious toxic effect of artemether. Then, the patient stopped the artemether treatment. After stopped the artemether treatment, the improvement of patient was also stopped. After restart artemether treatment, it successful improve the patient again (the patient NIHSS evaluation decreased to 18).

In conclusion, we reported that artemether treatment improved language and cognitive deficit of chronic ischemic stroke patient, these

evidences support the potential of artemisinin and its derivative artemether for the treatment of chronic ischemic stroke. In spite of the promising results, more studies are still necessary in order to collect more data to support t

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Conflict of Interest

The authors declare no conflict of interest.

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