ORIGINAL RESEARCH

Reduction of cerebrospinal fluid and plasma serotonin in patients with post-stroke depression: A preliminary report

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Abstract

Objective: To investigate the plasma and cerebrospinal fluid (CSF) concentrations of serotonin in patients with post-stroke depression (PSD).

Methods: Serotonin was measured in 30 PSD patients and 30 controls on day 15 and day 30 following stroke.

Result: There was a good correlation between the plasma and the CSF serotonin concentrations in both PSD ($r = 0.641$, $P = 0.001$) and control patients (0.852 , $P = 0.001$) 30 days following the stroke. The average plasma and CSF serotonin concentrations in the PSD patients were lower than in the control group on day 15 (CSF: 0.24 ± 0.27 vs 0.82 ± 0.48 $\mu\text{mol/L}$, $P < 0.01$; plasma, 0.32 ± 0.25 vs 0.83 ± 0.45 $\mu\text{mol/L}$, $P < 0.01$) and day 30 (CSF: 0.29 ± 0.23 vs 0.78 ± 0.47 $\mu\text{mol/L}$, $P < 0.01$; plasma, 0.31 ± 0.33 vs 0.89 ± 0.67 $\mu\text{mol/L}$, $P < 0.01$). Reduction of plasma serotonin was found in 90.0% of the PSD group and 13.3% of the control group patients ($P < 0.01$). Reduction in CSF serotonin in the PSD and control group was 80.0% and 6.7% respectively ($P < 0.01\%$).

Conclusion: Plasma serotonin levels may be used to represent the CSF serotonin levels in depressed and non-depressed patients following stroke. There is a reduction in the plasma or CSF serotonin concentrations in patients with PSD. Serotonin deficiency may be one of the factors leading to depression following stroke.

Stroke is a leading cause of morbidity and mortality in adults and is often associated with mental health disorders, such as depression, generalized anxiety or apathy. Post-stroke depression (PSD) is a common complication of stroke. Its prevalence has been reported to range from 17% to 47% three years after the stroke.¹⁻⁴

The etiology of PSD is not well understood. PSD is associated with physical disability and loss of function, but it cannot be explained simply as a response to the disability. The severity of depression correlates with proximity of the lesion to the left anterior frontal lobe^{5, 6}, while right hemisphere lesions show the reverse trend. Other factors that may contribute to the pathogenesis of PSD include decreased cerebral blood flow⁷, altered cortical receptor activity or abnormal concentration of cerebrospinal fluid (CSF) neurotransmitter metabolites.⁸

It has been hypothesized that during the acute brain infarction there is decreased monoamine synthesis, leading to decreased serotonin levels in the brain tissues.⁹ The evidence supporting this hypothesis has been that the PSD patients had a considerably lower

concentration of CSF 5-hydroxyindoleacetic acid (a serotonin metabolite) than the non-PSD patients.⁸ However, the actual CSF levels of serotonin have not been measured in PSD patients. This study sought to investigate the concentrations of serotonin in the post-stroke patients, and to assess the serotonin changes in patients who developed PSD. This study also sought to measure the plasma serotonin and to see if there is a correlation between the plasma and CSF concentrations of serotonin.

Patients and methods

This study was approved by the institutional review board. Written informed consent was obtained from all participants before the study. Patients who were hospitalized for first-time cerebral infarction (n=132) or haemorrhagic stroke (n=128) between January 2005 to January 2007 were approached by the investigators for participating the study. None of the patients had a diagnosis of depression before stroke. The diagnosis of stroke was confirmed in all patients by cranial CT scan and MRI. Patients who had clinically significant renal or hepatic dysfunction, cancer, cardiac arrhythmia, heart failure or uncontrolled hypertension were excluded from the initial screening. Unconscious patients or patients with severe cognitive impairment were also excluded from the study.

We used DSM-IV criteria for the diagnosis of depression due to stroke. We also used Hamilton rating scale (HAMD) to assess the severity of depression. Moderate to severe depression was considered when

the HAMD scores were more than 16, whereas a score of 7 to 16 was defined as a mild depression.

Among the 260 initial candidates, 52 (20%) had clinical depression at the initial screening, which took place within 10 days following the stroke. Out of the 52 candidates, 12 were excluded because they were unable to give a written consent or did not meet the enrolment criteria. In the end, 30 patients (PSD group) with HAMD score of more than 16 were selected from those who met the DSM-IV criteria for clinical major depression. Thirty stroke patients who had no clinical depression and whose HAMD score was < 7 were also selected from this cohort of patients to serve as the control group.

Venous blood samples and CSF were collected on day 15 and day 30 following the stroke. None of the patients of the study or control groups were prescribed with antidepressant within the first four weeks following the stroke.

Blood samples were centrifuged immediately after collection to separate plasma (1000g for 20 min at 4°C). High performance liquid chromatography (Waters Corp., MA, USA) with electrochemical detection was used for the determination of plasma or CSF concentrations of serotonin. Serotonin was measured with the methods reported previously by Cheng et al.¹⁰ The reference range in our laboratory for the plasma serotonin concentration was 0.28-1.10 µmol/L but the reference range for CSF serotonin was unavailable at the time of the study.

The data in the study were expressed as means ± SD. Student *t* test was used to analyse the differences in average age or serotonin concentrations between groups. Categorical data were analysed with Chi-square test. *P*<0.05 was considered statistically significant.

Results

There was no difference in age, sex or other baseline characteristics between the two groups (Table 1). The PSD patients were slightly younger but the average

TABLE 1. Baseline characteristics of patients.

	PSD group (n=30)	Control group (n=30)	<i>P</i>
Age	61.8±6.3	66.2±5.8	>0.05
Male/female	1 4/13	1 1/7	>0.05
Hypertension	12 (40.0%)	10 (33.3%)	>0.05
Diabetes	7 (23.3%)	7 (23.3%)	>0.05
Hyperlipidemia	7 (23.3%)	6 (20%)	>0.05
CAD	5 (16.7%)	7 (23.3%)	>0.05
Ischemic stroke	19 (63.3%)	17 (56.7%)	>0.05

PSD: post-stroke depression. CAD: coronary artery disease

TABLE 2. Comparison of serotonin concentrations between the PSD and control groups.

	PSD group ($\mu\text{mol/L}$)	Control group ($\mu\text{mol/L}$)	<i>P</i>
Day 15			
CSF	0.24 $\pm$ 0.27	0.82 $\pm$ 0.48	0.001
Plasma	0.32 $\pm$ 0.25	0.83 $\pm$ 0.45	0.001
Day 30			
CSF	0.29 $\pm$ 0.23	0.78 $\pm$ 0.47	0.001
Plasma	0.31 $\pm$ 0.33	0.89 $\pm$ 0.67	0.001

CSF: Cerebrospinal fluid. PSD: post-stroke depression.

age difference did not reach statistical significance (Table 1).

The average plasma or CSF concentrations of serotonin in the PSD group were lower than in the control group on day 15 or day 30 following the stroke (Table 2, $P < 0.01$). Using the reference range of plasma serotonin in our laboratory, reduction in serotonin was identified in 27 (90.0%) patients from the PSD group, and 4 (13.3%) patients from the control group 30 days after the stroke.

A good correlation between CSF and plasma serotonin concentrations was found in both PSD patients (Fig 1) and patients from the control group (Fig 2).

Since the average values of plasma and CSF serotonin were similar in the control group, we used the plasma reference range of serotonin to assess the appropriate serotonin levels in the CSF in both PSD and control groups. Reduction in CSF serotonin was identified in 80.0% (24/30) of the PSD group and 6.7% (2/30) of the control group 30 days after the stroke ($P < 0.01$).

Discussion

In blood, serotonin is present in high concentrations in platelets. It is released into plasma when platelets aggregate at sites of tissue damage.¹¹

In the central nervous system, serotonin is present in high concentrations in localized regions of the mid-brain, serving as a neurotransmitter.¹¹ The monoamine hypothesis of depression states that depression is

FIGURE 1. Study group. The correlation between the blood and cerebrospinal fluid (CSF) serotonin concentrations on day 15 (A) and day 30 (B) following the stroke.

FIGURE 2. Control group. The correlation between the blood and cerebrospinal fluid (CSF) serotonin concentrations on day 15 (A) and day 30 (B) following the stroke.

caused by a functional deficit of monoamine transmitters at certain sites in the brain.¹² Although serotonin has emerged as a key player in the pathogenesis of depression, results from the direct measurement of serotonin receptors in the post-mortem brain tissues have been inconsistent.¹² Investigations on the functional pathways involving serotonin in the depressed patients are inconclusive so far.¹²

Plasma 5-HT represents the equilibrium between 5-HT secretion, 5-HT catabolism (by monoamine oxidase enzyme activity in liver and lung), and platelet uptake mechanisms. Plasma concentration of serotonin can be influenced by several factors such as cancer, other chronic illnesses or medications. In healthy subjects, the plasma level of serotonin is about 0.62 μg/L; this was increased to an average of 6.3 μg/L in patients with intestinal cancer or hepatoma.¹³ Several groups have reported lowered plasma and platelet serotonin levels in patients with major depression.¹⁴

The levels of CSF or brain serotonin in patients with major depression disorder have been controversial. Some studies showed that major depression is associated with a reduced level of CSF serotonin and an increased level of serotonin turnover, as indicated by higher 5-hydroxyindoleacetic (a serotonin metabolite) acid/serotonin ratio.^{15,16} However, other studies found no differences in CSF concentrations of 5-hydroxyindoleacetic acid between depressed patients and healthy subjects, unless the depressed patients also had major panic disorder, in which case the turnover of serotonin was increased.^{17,18}

The present study focused on depression following a major cardiovascular event. We found that the serotonin concentration in the CSF in patients with PSD were considerably lower than in non-depressed patients. The proportion of patients with lower than normal serotonin concentrations in the PSD group was also higher than in the control group. In addition, the study also found that the average plasma concentra-

tion of serotonin in the PSD patients ($0.31 \mu\text{mol/L}$) were lower than in the non-depressed patients ($0.89 \mu\text{mol/L}$) 30 days following the stroke. These results indicate that deficiency in plasma or CSF serotonin may be related to the pathogenesis of PSD.

A unique aspect of the present study is that the plasma concentrations of serotonin seem to be closely related to the CSF concentrations in these stroke patients with or without depression. These results suggest that plasma concentrations of serotonin may be used to predict the CSF concentrations in patients with stroke or depression.

An inherent limitation of relating serotonin changes in the body fluid to the brain is that the concentrations of serotonin in the plasma or CSF may be influenced by several other factors, such as diet or drug treatment. In the present study, however, these factors did not seem to be of great importance. Dietary recommendations were consistent among our patients during hospitalization and after discharge. None of the participants were taking anti-depressants or other drugs that known to change the biosynthesis or metabolism of serotonin at the time of blood or CSF sampling.

Given the prevalence and importance of PSD, the effectiveness of antidepressant drugs in the management of PSD has been widely investigated. Selective serotonin re-uptake inhibitors (SSRIs), such as citalopram or sertraline, or noradrenaline reuptake inhibitors, such as nortriptyline or reboxetine, have been found safe and effective in treating PSD.^{19,20} Remission of PSD is associated with improvement in functional recovery.²¹ Therefore, early diagnosis and effective treatment of depression will help the rehabilitation outcome of stroke patients. The findings in the present study that PSD patients had lower plasma and CSF serotonin levels further support the use of SSRIs in the management of these patients.

In conclusion, this preliminary study demonstrates that the plasma or CSF concentration of serotonin is reduced in depressed patients following ischemic or hemorrhagic stroke. It also revealed that plasma and

CSF serotonin levels are similar and correlate well in both depressed and non-depressed patients. Further studies are warranted to assess the specific roles of serotonin reduction in the pathogenesis and management of depression following stroke.

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