Association between brain N-acetylaspartate levels and sensory and motor dysfunction in patients who have spinal cord injury with spasticity: an observational case-control study

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https://doi.org/10.4103/1673-5374.350216
Date of submission: December 17, 2021
Date of decision: February 19, 2022
Date of acceptance: March 21, 2022
Date of web publication: August 2, 2022

Abstract

Spinal cord injury is a severe and devastating disease, and spasticity is a common and severe complication that is notoriously refractory to treatment. However, the pathophysiologic mechanisms underlying spasticity and its development remain largely unknown. The goal of the present study was to find differences, if any, in metabolites of the left precentral gyrus and basal ganglia of patients who have spinal cord injury with or without spasticity, and to explore the relationship between the brain metabolite concentrations and clinical status. Thirty-six participants were recruited for magnetic resonance spectroscopic examination: 23 with spinal cord injury (12 with spasticity and 11 without spasticity) and 13 healthy controls. We acquired localized proton spectra from the precentral gyrus and basal ganglia via 10 mm3 voxels. Notably, univariate linear regression analysis demonstrated that the lower that the N-acetylaspartate concentration (a marker for neuronal loss) was in the precentral gyrus of the patients, the lower their ASIA (American Spinal Injury Association) light-touch scores, pinprick scores, and motor scores. Additionally, longer durations of injury were associated with higher N-acetylaspartate levels in the precentral gyrus. Compared with the healthy participants and patients without spasticity, N-acetylaspartate levels in the patients with spasticity were significantly lower in both the precentral gyrus and basal ganglia. Lower N-acetylaspartate levels also correlated with greater sensory and motor dysfunction in the patients who had spinal cord injury with spasticity.

Key Words: ASIA motor score; ASIA sensory score; basal ganglia; central nervous system; duration of injury; magnetic resonance spectroscopy; N-acetylaspartate; precentral gyrus; spasticity; spinal cord injury

Introduction

Spinal cord injury (SCI) is a severe and devastating disease that not only results in impaired motor and sensory function, and damage to the physiological, mental, and social well-being of the injured individuals, but also exerts a tremendous financial toll on families and the national healthcare system (Lynch and Cahalan, 2017; Toda et al., 2018; Choi et al., 2021; Shen et al., 2021). Approximately 60–80% of individuals with SCI suffer from secondary spasticity, and the prevalence of problematic spasticity has been reported to be around 35–40% (Holtz et al., 2017; Skoog and Jakobsson, 2020). Long-lasting spasticity commonly impairs quality of life, causes involuntary movements, pain, and fatigue, disturbs sleep, contributes to the development of contracture, infection, and pressure ulcer, hampers social interactions and rehabilitation efforts, and severely interferes with activities of daily living (van Cooten et al., 2015; Holtz et al., 2017).

Magnetic resonance spectroscopy (MRS) is an advanced imaging technology that can noninvasively assess and quantify the concentrations of various cellular metabolites in vivo, and reveal information concerning the biochemical composition of different brain regions. The tissue metabolites generally evaluated include N-acetylaspartate (NAA), choline (Cho), creatine (Cr), glutamine (Gln), myo-inositol (MI), and gamma-aminobutyric acid (GABA) (Chang et al., 2013).

Past studies of patients with SCI and neuropathic pain have reported a reduction of NAA in either the anterior cingulate cortex (Widerstrom-Noga et al., 2013) or the thalamus (Pattany et al., 2002; Gustin et al., 2014), which was negatively correlated with pain intensity (Pattany et al., 2002). Another SCI study demonstrated a decrease in spinal cord NAA, which might have been associated with greater loss of spinal cord area in pain-free patients with SCI (Pfyffer et al., 2020). Most studies agree that after damage to the spinal cord, spasticity is associated with injury of the descending motor pathways, notably...
the corticospinal and reticulospinal pathways (Trampop et al., 2014; Lee et al., 2016), but few studies have examined the contribution of subsequent neural and biochemical abnormalities in the central nervous system (CNS) to spasticity after SCI, which remains poorly understood. Hence, application of MRS might reveal a potential central mechanism of spasticity after SCI we hypothesize that changes in brain metabolites are involved in the generation and maintenance of spasticity after SCI, and that they correlate with clinical data as well as the duration of injury, motor deficits as assessed by American Spinal Injury Association (ASIA) scores.

Methods

This observational study was carried out in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the China Rehabilitation Research Center on August 1, 2020 (Approval No. 2020-019-1). Written informed consent was obtained from all participants. The writing and editing of the research article were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (von Elm et al., 2007). This study was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR1900026922) on October 26, 2019 and with the National Health Security Information Platform, medical research registration, and filing information system (Registration No. MR-11-21-013247) on January 28, 2021.

Participants

Patients with SCI (n = 33) were recruited from the Department of Spinal and Neural Function Reconstruction at the China Rehabilitation Research Center in Beijing from March 1, 2021 to August 1, 2021, and healthy control participants (n = 13) were recruited by advertisement on The Internet. Due to the absence of a control group, we compared patients with SCI to the exclusion criteria during the study period. The clinical data were collected from March 1, 2021 to August 10, 2021. The spasticity of the patients was examined using MAS, and the participants with SCI were subsequently divided into a non-spastic group (MAS = 0; n = 11) and spastic group (MAS = 1, 2, or 3; n = 12) according to their MAS scores (Bohannon and Smith, 1987). All members of the spastic group were under the same antispastic medication (baclofen 75 mg per day, Novartis Farma S.p.A., Italy).

The inclusion criteria for the patients with SCI were as follows: 1) SCI; 2) aged between 18 and 60 years; 3) right-hand dominant. The exclusion criteria were: 1) history of CNS diseases such as intracranial tumors, traumatic brain injury, or epilepsy; 2) current or historical drug abuse or long-term heavy alcohol use; 3) current or past psychiatric problems such as schizophrenia, depression, or severe anxiety; 4) significant cognitive deficits measured by Raven Standard Intelligence Test; 5) contraindicated for magnetic resonance imaging (MRI) examination (i.e., an incompatible cardiac pacemaker, an aneurysm clip, a ferromagnetic implant, or claustrophobia), or inability to complete a 3T MRI scan. Because SCI is usually caused by vehicular accident, fall from a great height, or being crushed by a heavy weight, patients with SCI often suffer from concomitant brain trauma. Such brain damage was assessed based on a conventional MRI scan, a careful physical examination upon admission, and medical history, and patients were excluded under criterion 1 above. Attention was particularly paid to symptoms such as transient disturbance of consciousness, eczema, headache, and vomiting. In addition to standard demographic information—e.g., age, gender, etiology of injury—the extent of motor and sensory impairment was assessed by a single qualified clinician using the ASIA classification scale (Asia and Committee, 2019). Healthy participants were also right-hand dominant and were excluded if they had a diagnosis of concomitant brain trauma based on a conventional MRI scan. There was no difference in age or gender among the three groups. The enrollment and allocation of participants are shown in Figure 1.

MRS data acquisition

The study was performed at the China Rehabilitation Research Center in Beijing using a 3.0 Tesla MRI scanner (Philips Ingenia, Best, Netherlands) with a standard head coil for both MRS and MRS measurements. The patients lay in the scanner in a head-first supine position. We acquired T2-weighted images from all participants before the MRS examination, and separately centered a voxel (10 mm³) of interest in the left precentral gyrus (PG) (Figure 2A, C, and E) and the basal ganglia (BG) (Figure 2B, D, and F). The region of interest for the PG was anterior to the central sulcus, and that for the BG was adjacent to internal capsule, and the exact location was determined by a single experienced radiologist who was completely unaware of the experimental grouping. MR spectra of all participants were measured with a stimulated echo acquisition mode (STEAM) sequence with the following parameters: repetition time 2200 ms, echo time 220 ms, field of view 20 cm, matrix size 128 × 128, bandwidth = 2 kHz, acquisition points = 1024, and total acquisition time ≈ 836 seconds. We performed shimming using manufacturer-supplied shimming procedures. Water suppression was applied by placing frequency-selective excitation pulses at the frequency of the MRS sequence. The absolute concentrations of NAA, MI, Cho, and Cr were estimated by dividing the pixel area under the peaks by the water peak area. The metabolite concentrations are expressed as mmol/kg.

Statistical analysis

Statistical analysis was performed using SPSS software, version 26.0 (IBM Corp, Armonk, NY, USA). Comparisons in age and gender between spastic, non-spastic, and healthy control groups were conducted using ANOVA or the chi-square tests, as appropriate.

Differences in ASIA light-touch score were tested using an independent-samples t-test. Differences in ASIA pinprick score, ASIA motor score, and the duration of injury did not conform to the normal distribution, and were thus analyzed using the Mann-Whitney U test. Differences in the MRS spectra and ASIA scores between the spastic and non-spastic groups were examined via chi-square tests. A univariate linear regression analysis was performed between the concentration of NAA in the PG and BG and clinical data (ASIA light-touch score, ASIA pinprick score, ASIA motor score, and the duration of injury) to investigate the relationships between the variance in NAA concentration and clinical variables. Continuous variables are reported as the mean ± SD. Differences in NAA values between the spastic, non-spastic, and healthy control group were compared using the Kruskal-Wallis test, and differences in MRS metabolite concentrations between the SCI and control groups were compared using independent-samples t-tests. P values of less than 0.05 were considered to be statistically significant.

Results

MRS data were acquired from the left PG and left BG from all participants. Demographic and clinical characteristics of all participants are shown in Table 1.

Relationships between NAA concentration and clinical data

Univariate linear regression analysis demonstrated that lower NAA concentration in the PG was significantly associated with lower ASIA light-touch score (β = 468.81, 95% Confidence Interval [CI]: 33.53–71.67, P = 0.002) (Figure 4A), ASIA light-touch scores (β = 258.39, 95% CI: 28.67–35.50, P = 0.001) (Figure 4B), ASIA right light-touch scores (β = 210.42, 95% CI: 22.65–28.83, P = 0.002) (Figure 4C), ASIA pinprick scores (β = 338.49, 95% CI: 21.77–32.58, P = 0.002) (Figure 4E), ASIA right pinprick scores (β = 307.25, 95% CI: 23.56–33.48, P = 0.002) (Figure 4F), ASIA motor scores (β = 419.89, 95% CI: 49.15–58.76, P < 0.001) (Figure 4G), ASIA left motor scores (β = 307.31, 95% CI: 23.80–31.59, P = 0.004) (Figure 4H), and ASIA right motor scores (β = 210.68, 95% CI: 22.65–28.83, P = 0.003) (Figure 4I). Furthermore, longer durations of injury were associated with greater NAA levels in the PG (β = 0.001, 95% CI: 0.083–0.105, P = 0.001) (Figure 4J). However, no significant relationships were observed between NAA levels in the BG and any of the other clinical data (ASIA motor score, ASIA light-touch score, and ASIA pinprick score). Furthermore, no relationships were found between the other metabolites (MI, Cho, and Cr) and any of the clinical data (ASIA motor score, ASIA light-touch score, ASIA pinprick score, and the duration of injury).

Difference of NAA concentration

Though no difference in NAA value was observed between the SCI group and the control group in the left PG (P = 0.174) or BG (P = 0.818) (Figure 5A), levels were significantly lower in the spastic group than in either the non-spastic group (P = 0.001) or the control group (P = 0.001) (Figure 5B). However, values in the non-spastic group and the control group were comparable (P = 0.119) (Figure 5B). The same pattern was found for NAA concentration in the left BG: NAA levels were significantly lower in the spastic group than in the non-spastic group (P = 0.001) or the control group (P = 0.001) (Figure 5C), but not comparable between the non-spastic and control groups (P = 0.119; Figure 5C). Additionally, no differences were found with regard to the other metabolites between the spastic and non-spastic groups or the SCI and control groups (all P > 0.05).

Figure 1 | Flow diagram of the trial design.

MRI: Magnetic resonance imaging; MRS: magnetic resonance spectroscopy; SCI: spinal cord injury.
The relationship between NAA concentration in the PG and clinical data.

Figure 2 | Magnetic resonance spectroscopic images for patients with SCI and spasticity, patients with SCI but no spasticity, and healthy controls. 

(A–F) Sagittal, axial, and coronal T1-weighted images showing the location of the 10-mm³ voxel (at the crosshairs) in the left precentral gyrus (PG) (A) and left basal ganglia (BG) (B) of a patient with SCI and spasticity, the left PG (C) and left BG (D) of a patient with SCI but no spasticity, and the left PG (E) and left BG (F) of a healthy participant. The region of interest in the PG was adjacent to central sulcus, and that in the BG was adjacent to internal capsule. The exact location was determined by a single experienced radiologist who was completely unaware of the experimental grouping. SCI: Spinal cord injury.

Figure 3 | Magnetic resonance spectroscopic results for the three groups. 

Typical single-voxel stimulated echo acquisition mode (STEAM) spectra acquired from the left PG (A) and left BG (B) of a patient with SCI and spasticity, the left PG (C) and left BG (D) of a patient with SCI but no spasticity, and the left PG (E) and left BG (F) of a healthy participant. Spectral analysis is described in the Methods section. BG: Basal ganglia; PG: Precentral gyrus; SCI: Spinal cord injury.

Figure 4 | The relationship between NAA concentration in the PG and clinical data. 

(A–I) Univariate linear regression analysis demonstrated correlations between NAA concentration in the PG, and ASIA light-touch score (A), ASIA left light-touch score (B), ASIA right light-touch score (C), ASIA pinprick score (D), ASIA left pinprick score (E), ASIA right pinprick score (F), ASIA motor score (G), ASIA left motor score (H), and ASIA right motor score (I). (J) Univariate linear regression analysis showing that NAA concentration in the PG increased with duration of injury. ASIA: American Spinal Injury Association; NAA: N-acetylaspartate; PG: Precentral gyrus.

Figure 5 | Group differences in NAA concentration. 

(A) Differences in NAA concentration in the left PG and left BG between the SCI group and the healthy control group. (B, C) NAA concentration in the left PG (B) and left BG (C) for all three groups. BG: Basal ganglia; NAA: N-acetylaspartate; PG: Precentral gyrus; SCI: Spinal cord injury.
Table 1  |  Demographic and clinical characteristics

| Characteristics | SCI (n = 23) | SCI-Spastic (n = 12) | SCI-Non-spastic (n = 11) | Healthy control (n = 13) | P-value SCI vs. Con | P-value spas vs. non-spas | P-value spas vs. non-spas vs. Con |
|----------------|-------------|---------------------|-------------------------|-----------------------|---------------------|------------------------|-----------------------------|
| Handedness      | 23(100)/0   | 12(100)/0           | 11(100)/0               | 13(100)/0            | 1                   | 1                      | 1                           |
| Age (yr)        | 34.87±10.93 | 39.83±6.80          | 29.45±6.80              | 33.00±8.71           | 0.626               | 0.058                  | 0.091                       |
| Sex (male/female)| 18(78.3)/5(21.7) | 9(75.0)/3(25.0) | 9(81.8)/2(18.2)        | 9(69.2)/4(30.8)      | 0.548               | 0.890                  | 0.091                       |
| ASIA motor score| 50.25±10.46 | 58.00±10.79         | 50.25±10.46             | 0.091                | 0.091               | 0.091                  | 0.091                       |
| ASIA light-touch score| 60.42±16.54 | 70.73±11.05         | 60.42±16.54             | 0.096                | 0.096               | 0.096                  | 0.096                       |
| ASIA pinprick score| 46.92±22.85 | 65.36±20.01         | 46.92±22.85             | 0.091                | 0.091               | 0.091                  | 0.091                       |
| Etiology        |             |                     |                         |                      |                     |                        |                             |
| Vehicle accident | 6(26.1)     | 3(25.0)             | 3(27.3)                 | 6(26.1)              | 6(26.1)             | 6(26.1)                | 6(26.1)                     |
| Fall            | 9(39.1)     | 5(41.7)             | 4(36.4)                 | 9(39.1)              | 9(39.1)             | 9(39.1)                | 9(39.1)                     |
| Crush by weight | 4(17.4)     | 3(25.0)             | 3(27.3)                 | 4(17.4)              | 4(17.4)             | 4(17.4)                | 4(17.4)                     |
| Sport injury    | 1(4.3)      | 0                   | 1(9.1)                  | 1(4.3)               | 1(4.3)              | 1(4.3)                 | 1(4.3)                      |
| Others          | 3(13.0)     | 1(8.3)              | 2(18.2)                 | 3(13.0)              | 3(13.0)             | 3(13.0)                | 3(13.0)                     |
| Injured level   |             |                     |                         |                      |                     |                        |                             |
| C               | 7(30.4)     | 6(50.0)             | 7(53.8)                 | 7(30.4)              | 7(30.4)             | 7(30.4)                | 7(30.4)                     |
| T               | 15(65.2)    | 6(50.0)             | 9(81.8)                 | 15(65.2)             | 15(65.2)            | 15(65.2)               | 15(65.2)                    |
| L               | 1(4.3)      | 0                   | 1(9.1)                  | 1(4.3)               | 1(4.3)              | 1(4.3)                 | 1(4.3)                      |
| ASIA            |             |                     |                         |                      |                     |                        |                             |
| A               | 10(43.5)    | 6(50.0)             | 4(36.4)                 | 10(43.5)             | 10(43.5)            | 10(43.5)               | 10(43.5)                    |
| B               | 3(13.0)     | 1(8.3)              | 2(18.2)                 | 3(13.0)              | 3(13.0)             | 3(13.0)                | 3(13.0)                     |
| C               | 8(34.8)     | 4(33.3)             | 4(36.4)                 | 8(34.8)              | 8(34.8)             | 8(34.8)                | 8(34.8)                     |
| Duration of injury (min) | 2(8.7) | 1(8.3) | 1(9.1) | 2(8.7) | 2(8.7) | 2(8.7) | 2(8.7) |

Data are expressed as number (percentage) or mean ± SD as appropriate. ASIA: American Spinal Injury Association; Con: healthy controls; SCI: spinal cord injury; spas: spasticity.

Discussion

In our examination, two brain regions which were implicated in spasticity were chosen to determine whether metabolic abnormalities are related to spasticity. Spasticity is generally considered a syndrome of upper motor neuron dysfunction mainly in the PG and projecting to lower motor neurons via the spinal cord through the BG, which has important connections with cortical regions. MRS sequencing was performed in the left PG and left BG, which have been suggested as the primary sites where lesions induce spasticity (Mukherjee and Chakravarty, 2010). Accordingly, impairment of axons/neurons in the PG and BG might be involved in the formation and maintenance of spasticity following SCI. Because patients with SCI often suffer from spasticity and/or neuropathic pain, they cannot tolerate a prolonged period of MRS scanning. Therefore, we did not attempt bilateral examinations. The finding that NAA concentration in the encephalic region did not differ between the left and right hemispheres supports the idea that NAA measurements from one hemisphere are representative of both (Pattany et al., 2002). Because all patients were right-handed, we chose the PG and BG of the left hemisphere when searching for changes in brain metabolites after SCI.

As a dominating metabolic feature, NAA is the most important and frequently used parameter in MRS studies. Under normal conditions, the most prominent NAA peak arises at 2.0 ppm. Synthesized in neuronal mitochondria, NAA is the most abundant free amino acid in CNS (Moffett et al., 2007). Though its function is not yet fully known, NAA is speculated to function as both a precursor and metabolite of N-acetylaspartylglutamate (NAAG; also called N-Acetylaspartylglutamic acid), a regulator of protein synthesis and storage of aspartate or acetyl-CoA, and as an osmolyte of neurons (Tsai and Coyle, 1995; Barker, 2001). As immunocytochemical studies have indicated that NAA is almost exclusively located in neurons and neuronal processes within the mature cerebral cortex, NAA serves as a perfect surrogate marker of neuronal density (Smith et al., 2012; Rae, 2014). Therefore, a reduction in NAA is generally believed to represent neuronal loss (Pego et al., 2012; Widerstrom-Noga et al., 2016). The present study observed that NAA concentrations were lower in patients with spasticity than in those without. However, there were no differences in age, gender, ASIA sensory or motor scores, level of injury, or injury level.

The present study demonstrated that lower NAA concentration in left PG of the patients with SCI was associated with increasing clinical severity of injury, as assessed by lower ASIA light-touch, pinprick, and motor scores. Irreversible structural and metabolic damage to the motor and sensory neurons above the level of injury is likely to occur in SCI, which results in a prominent decline of neuronal population and therefore low levels of NAA upon MRS examination. The loss of PG neurons could reflect widespread impairment throughout the entire cerebral cortex, including the postcentral gyrus, which would explain why, in addition to lower ASIA motor scores, lower NAA concentration in the PG was also associated with lower light-touch and pinprick scores. Previous studies of a variety of CNS injuries have suggested that lower NAA levels are associated with worse neuronal outcomes (Craciunas et al., 2013; Wyss et al., 2019). Therefore, as we observed, the degree to which NAA levels are lower than normal in the PG should be most marked in patients with the most prominent motor and sensory loss. Thus, NAA concentration potentially reflects clinical signs and symptoms and serves as a potential biomarker for prognosis.

Another point to emphasize is that increased duration of injury might be associated with rising NAA levels in the PG, indicating that cortical reorganization itself is not static, and that changes in NAA levels and the regeneration of neurons is a dynamic process (Freund et al., 2013). Although neurons in the CNS are notorious for their limited ability to regenerate (Boroojerdi et al., 2007), MRS has not generally been considered necessary for routine clinical application because the metabolic changes detected tend to be trivial and the clinical significance is not fully appreciated. However, MRS can not only reveal neurochemical changes that precede structural and functional alterations (Boroojerdi et al., 2007) but can also point to pathophysiological processes in the brain even in the absence of visible signs of cerebral involvement on conventional MRI.
our finding that preserved NAA is related to less spasticity as well as better sensory and motor prognosis in patients with SCI, MRS can be a valuable investigative technique for early detection of neuronal loss, prediction of spasticity or remaining neuronal function, and evaluation of treatment effects in clinical trials.

The present study had some limitations that should be considered when interpreting the results. Further study should include a larger sample, and longitudinal studies should be performed to look at serial changes in NAA within the same individuals. In addition, studies concerning the underlying pathophysiological mechanism of neuronal loss after SCI both in vivo and in vitro should be performed.

Conclusion

The results of this study indicate that as NAA serves as a neuronal marker, neuronal loss in the CNS likely contributes to poorer ASIA sensory and motor scores. Neuro-regeneration probably takes place as time passes after injury. Patients with SCI and spasticity might have a higher degree of neuronal loss than those without spasticity.

Acknowledgments: We are grateful to China Rehabilitation Research Center (CRRC) for their support, and also to our colleagues from Department of Spinal and Neural Function Reconstruction; Chinese Institute of Rehabilitation Science; Center of Neural Injury and Repair; Beijing Key Laboratory of Neural Injury and Rehabilitation, CRRC for their technical support, modification advice, and statistical recommendations.

Author contributions: Study design, recruitment, and statistical analysis: JYL; recruitment: FG, YIL, XZ; MRS data acquisition: XCY, YIL, JYL; study guidance: JYL, FG, ZT. All authors approved the final version of paper.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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