

Guanidinoacetate–creatine in secondary progressive multiple sclerosis: a case report

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Abstract

Acute secondary progressive multiple sclerosis (SPMS) is characterized by escalating neurological disability, with limited disease-modifying therapeutic options. A 48-year-old woman with acute SPMS being treated with interferon beta-1a and oral corticosteroids presented as a clinical outpatient with no disease-modifying effects after treatment. A decision was made to treat her with a combination of guanidinoacetate and creatine for 21 days. She had made clinical progress at follow-up, with the intensity of fatigue dropping from severe to mild. Magnetic resonance spectroscopy revealed increased brain choline, creatine, N-acetylaspartate, and glutathione. Patients with SPMS may benefit from guanidinoacetate–creatine treatment in terms of patient- and clinician-reported outcomes; this requires additional study.

Keywords

Multiple sclerosis, creatine, guanidinoacetic acid, brain metabolism, case report, patient outcome

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Introduction

Conversion to secondary progressive multiple sclerosis (SPMS) is associated with a relatively poor prognosis, partly owing to the limited effects of the available disease-modifying therapies in progressive disease.¹ Among other features, SPMS is accompanied by unfavorable brain metabolism changes that lead to diffuse neuroaxonal

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loss and clinical deterioration during the disease course.² Reprogramming of energy metabolism has emerged as a promising therapeutic approach in MS.³ Specifically, a disease-driven brain creatine deficit can be seen as a distinctive pathological facet in severe MS that might be approached with targeted therapies to restore creatine homeostasis in cerebral tissue (for a detailed review, see Ref. 4). Among potential therapeutic candidates, guanidinoacetate (GAA, also known as guanidinoacetic acid or glycyamine) has recently been identified as a direct precursor of creatine that may favorably upregulate location-specific brain creatine concentrations in white matter.⁵ Interestingly, a GAA–creatine mixture has been found to be superior to creatine itself in effectively improving bioenergetics in the human brain,⁶ perhaps owing to the unique transportability features of this combination in the nervous system.⁷

Case presentation

A 48-year-old woman with SPMS being treated with interferon beta-1a and oral corticosteroids presented as a clinical outpatient with no disease-modifying effects after treatment and rapidly progressive fatigue. She had completed two cycles of combination therapy in the past 6 months and noted no significant decreases in muscle spasms, numbness, weakness, or tremor in one or both arms and legs. The patient was diagnosed with the disease at age 30 years, and a secondary progressive phenotype developed approximately 3 years prior to the current admission. Initially, MS was diagnosed as a relapsing–remitting type, characterized by periods of active symptoms (e.g., fatigue, tingling, pronounced reflexes, cognitive impairment) alternating with periods of less severe symptoms.

At the initial examination on admission, the patient reported a current episode of SPMS with moderate-to-severe weakness

or increased spasticity (including mono- and paraparesis), dysdiadochokinesia, and problems with the heel-to-shin test, bladder incontinence, and severe general fatigue. Use of a visual analog scale (VAS) for SPMS symptoms revealed high scores for weakness (9.5 out of 10) and depression/anxiety (7.5 out of 10). Her brain magnetic resonance (MR) imaging showed diffuse multinodular demyelination areas in the cerebral cortex, midbrain, and cerebellum, accompanied by impaired metabolism illustrated by low levels of creatine (4.51 mM), choline (1.05 mM), N-acetylaspartate (NAA, 7.37 mM), and glutathione (0.13 mM) and high glutamate (8.35 mM) in the gyrus cinguli as evaluated with single-voxel ¹H MR spectroscopy (Figure 1a). MR imaging and spectroscopy were performed using a 1.5T scanner (Siemens Avanto Tim, Erlangen, Germany) with a matrix head coil (receiver coil) in circularly polarized mode. The MR protocol included: (a) sagittal T1-weighted spin-echo sequence with repetition time to echo time (TR/TE) of 511/8.7 ms, (b) axial T2-weighted turbo spin-echo (TSE) sequence with TR/TE of 8590/98 ms, (c) coronal T2 TSE TR/TE 5170/105 (3.0-mm slice thickness), and (d) axial fluid-attenuated inversion recovery with TR/TE 8840/109 (5.0-mm slice thickness). A single-voxel data set was acquired with point-resolved spectroscopy TR/TE 1500/30. A volume of interest (VOI) for MR spectroscopy, measuring 15 × 15 × 15 mm located in the anterior cingulate gyrus, was acquired using 256 averages. Non-water-suppressed data were also obtained with the same geometric parameters (64 averages) to provide an internal water reference for the absolute quantification of metabolites. Interfering signal contributions from areas outside the VOI were suppressed by six saturation regions, manually positioned along the margin of each VOI. The homogeneity of the magnetic field was

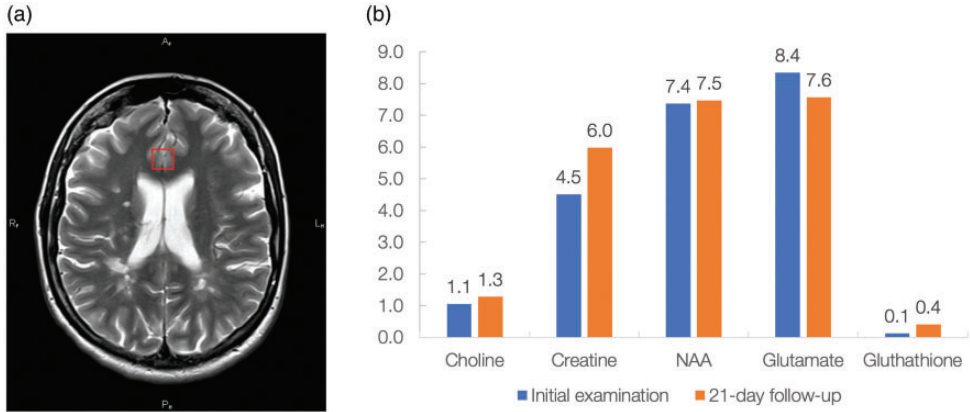


Figure 1. Magnetic resonance (MR) imaging showing (a) diffuse multinodular demyelination areas in the brain of the patient, with red square indicating a specific area (gyrus cinguli) for MR spectroscopy assessment of selected brain metabolites, (b) at initial examination and 21-day follow-up after guanidinoacetate–creatine intervention (concentration shown in mM). NAA, N-acetylaspartate.

optimized using manual shimming. We changed the shim currents to obtain as-small-as-possible full width at half maximum (FWHM) and as-large-as-possible T2. Using interactive shimming to check and improve the quality of spectra, we obtained an FWHM less than 15 Hz for all peaks measured (e.g., 3.03 ppm creatine and 2.01 ppm NAA both pre- and post-treatment). Quantification of the single-voxel spectroscopy data was performed offline using the TARQUIN software package.⁸ The post-processing protocol included: water reference processing by averaging 20 adjacent points, removing the residual water signal from the spectrum by subtracting it from the time signal and frequency shift correction of the water signal, Hanning filter 512-ms width, zero-filling from 512 to 1024 data points, and Fourier transformation. Absolute concentrations of creatine, choline, NAA, glutamate, and glutathione were calculated using water signals from the identical voxel as an internal reference. Cramér–Rao lower bounds (CRLB) for individual metabolite estimates of baseline and

follow-up measures are provided in Supplementary Table 1. The signal-to-noise ratio for pre- and post-treatment MR spectroscopy data was 81.7 and 78.5 for creatine, and 135.1 and 132.6 for NAA, respectively.

Numerous lines of evidence point to the possibility that creatine depletion,⁹ glutamate toxicity,¹⁰ and low glutathione¹¹ in the brain might contribute to various types of MS (including SPMS), likely leading to the loss of brain volume and symptomatology of the disease. Our patient's routine biochemistry revealed no significant disturbances in blood urea nitrogen, inflammatory markers, lipid profiles and glucose, or clinical enzymes. Given the limited effects of current treatments and the clinical presentation, a decision was made to treat her with a combination of oral GAA and creatine (4 g per day, 2:2 ratio) for 21 days. She made moderate clinical progress at follow-up, with the intensity of general fatigue dropping from severe to mild and VAS scores for weakness and numbness dropping by 1.25 points, on average, using a 10-point scale; her depression/anxiety

scores remained identical to the baseline values. MR spectroscopy revealed increased brain choline, total creatine, NAA, and glutathione, and a drop in glutamate levels at 21-day follow-up compared with levels at initial examination (Figure 1b). The patient reported no side effects of the intervention, as evaluated using an open-ended questionnaire administered during the treatment.

The design of this study was approved by the local institutional review board at the University of Novi Sad (#46-06-02/2020-1). The study was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization Efficacy Guidelines E6. Written informed consent was obtained from the patient before the experimental treatment with oral GAA and creatine was administered. The reporting of this study conforms to the CARE guidelines.¹²

Discussion

We confirmed that a GAA–creatine formulation augmented creatine concentrations at the gyrus cinguli in a patient with SPMS. This was accompanied by a rise in brain glutathione and mild elevation in NAA, implying a relatively favorable metabolic milieu post-administration. However, the increase in brain choline found after the intervention might indicate possible gliosis and/or hidden lesioning,^{13,14} requiring caution and further investigation. Given that the spectral fitting of MR spectroscopy has a more significant CRLB than the difference in metabolic outcomes,¹⁵ no firm conclusions can be drawn, but the results remain very promising. Additionally, our patient reported easing of symptoms (including fatigue, weakness, and numbness) when many other SPMS therapies had failed. This is in accordance with another randomized controlled trial suggesting that GAA is a potent approach to tackling general fatigue in clinical

patients.¹⁶ Although the subjective nature of the symptoms and study design somewhat limit the scope and significance of the present findings, including the lack of past or current Expanded Disability Status Scale scores, the GAA–creatine mixture remains worthy of further scrutiny in MS and perhaps other white matter disorders.

In conclusion, patients with SPMS may benefit from 21-day GAA–creatine treatment in terms of patient- and clinician-reported outcomes. The present study findings require further investigation in well-powered randomized controlled trials.

Authors' contributions

SMO: research design (project conception, development of overall research plan, and study oversight); analyzed the data and performed the statistical analysis; wrote the article draft; and had primary responsibility for the final content. JO, DZ, TJ and VS: conducted the research; analyzed the data and performed the statistical analysis; wrote the article draft; and revised the paper. All authors read and approved the final manuscript.

Declaration of conflicting interest


The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SMO serves as a member of the Scientific Advisory Board on Creatine in Health and Medicine (AlzChem LLC). SMO owns the patent “Sports Supplements Based on Liquid Creatine” registered with the European Patent Office (WO2019150323 A1) and has an active patent application, “Synergistic Creatine” submitted to the UK Intellectual Property Office (GB2012773.4). SMO has served as a speaker at Abbott Nutrition, a consultant for Allied Beverages Adriatic and IMLEK, and an advisory board member of the University of Novi Sad School of Medicine. SMO has received research funding related to creatine from the Serbian Ministry of Education, Science, and Technological Development, Provincial Secretariat for Higher Education and Scientific Research, AlzChem GmbH, KW Pfannenschmidt GmbH,

ThermoLife International LLC, and Monster Energy Company. SMO is an employee of the University of Novi Sad and does not own stocks and shares in any organization. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. JO, DZ, TJ, and VS declare no conflicts of interest.

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References

1. Lorscheider J, Buzzard K, Jokubaitis V, et al. Defining secondary progressive multiple sclerosis. *Brain* 2016; 139: 2395–2405. doi: 10.1093/brain/aww173.
2. Obert D, Helms G, Sättler MB, et al. Brain metabolite changes in patients with relapsing-remitting and secondary progressive multiple sclerosis: a two-year follow-up study. *PLoS One* 2016; 11: e0162583. doi: 10.1371/journal.pone.0162583.
3. Vallée A, Lecarpentier Y, Guillemin R, et al. Demyelination in multiple sclerosis: reprogramming energy metabolism and potential PPAR γ agonist treatment approaches. *Int J Mol Sci* 2018; 19: 1212. doi: 10.3390/ijms19041212.
4. Ostojic SM. Creatine and multiple sclerosis. *Nutr Neurosci* 2020; 1–8. Online ahead of print. doi: 10.1080/1028415X.2020.1819108.
5. Ostojic SM. Guanidinoacetic acid loading for improved location-specific brain creatine. *Clin Nutr* 2021; 40: 324–326. doi: 10.1016/j.clnu.2020.05.003.
6. Semeredi S, Stajer V, Ostojic J, et al. Guanidinoacetic acid with creatine compared with creatine alone for tissue creatine content, hyperhomocysteinemia, and exercise performance: a randomized, double-blind superiority trial. *Nutrition* 2019; 57: 162–166. doi: 10.1016/j.nut.2018.04.009.
7. Ostojic SM. Co-administration of creatine and guanidinoacetic acid for augmented tissue bioenergetics: A novel approach? *Biomed Pharmacother* 2017; 91: 238–240. doi: 10.1016/j.biopha.2017.04.075.
8. Wilson M, Reynolds G, Kauppinen RA, et al. A constrained least-squares approach to the automated quantitation of in vivo ^1H magnetic resonance spectroscopy data. *Magn Reson Med* 2011; 65: 1–12. doi: 10.1002/mrm.22579.
9. Hanefeld F, Bauer HJ, Christen HJ, et al. Multiple sclerosis in childhood: report of 15 cases. *Brain Dev* 1991; 13: 410–416. doi:10.1016/s0387-7604(12)80038-6.
10. Azevedo CJ, Kornak J, Chu P, et al. In vivo evidence of glutamate toxicity in multiple sclerosis. *Ann Neurol* 2014; 76: 269–278. doi: 10.1002/ana.24202.
11. Choi IY, Lee SP, Denney DR, et al. Lower levels of glutathione in the brains of secondary progressive multiple sclerosis patients measured by ^1H magnetic resonance chemical shift imaging at 3 T. *Mult Scler* 2011; 17: 289–296. doi: 10.1177/1352458510384010.
12. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547. doi: 10.1111/head.12246.
13. He J, Inglese M, Li BS, et al. Relapsing-remitting multiple sclerosis: metabolic abnormality in nonenhancing lesions and normal-appearing white matter at MR imaging: initial experience. *Radiology* 2005; 234: 211–217. doi: 10.1148/radiol.2341031895.
14. Inglese M, Liu S, Babb JS, et al. Three-dimensional proton spectroscopy of deep gray matter nuclei in relapsing-remitting MS. *Neurology* 2004; 63: 170–172. doi: 10.1212/01.wnl.0000133133.77952.7c.
15. Kreis R. The trouble with quality filtering based on relative Cramér-Rao lower bounds. *Magn Reson Med* 2016; 75: 15–18. doi: 10.1002/mrm.25568.
16. Ostojic SM, Stojanovic M, Drid P, et al. Supplementation with guanidinoacetic acid in women with chronic fatigue syndrome. *Nutrients* 2016; 8: 72. doi: 10.3390/nu8020072.