Glutamate-based magnetic resonance spectroscopy in neuroleptic malignant syndrome

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Abstract

Glutamate neurotoxicity is implicated in a number of neurological diseases, including Neuroleptic Malignant syndrome. Therefore, functional magnetic resonance imaging can help in diagnosis and monitoring such conditions. However, reports of this application are scarce in the literature. In this manuscript, glutamate based imaging of the basal ganglia showed increased levels of the neurotransmitter bilaterally. In addition, a radon transform of the functional image was performed to look for any asymmetry in cerebral activation. Although no asymmetry was detected in this case, this novel analysis can be applied in physiological and pathological scenarios to visualize contribution of different brain structures.

Key Words

Glutamate, magnetic resonance spectroscopy, neuroleptic malignant syndrome

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Introduction

Glutamate is one of the most ubiquitous neurotransmitters in the brain and it has been clearly implicated in Neuroleptic Malignant syndrome (NMS).[1] A rapid rise in intracerebral levels of glutamate in NMS results in features of hyperthermia, severe hypertonia, and tremors. Although, intracerebral concentration of glutamate is being investigated with proton-based magnetic resonance spectroscopy (HMRS) in cognitive decline,[2] Alzheimer's disease,[3] and autistic spectrum disorders,[4] to the best of our knowledge, there are no reports of similar efforts in NMS.

It can be rationally hypothesized that HMRS would reveal an increased concentration of glutamate in the basal ganglia in a patient of NMS. Here, we report the case of a patient of NMS, in whom HMRS proved this hypothesis. This report is a proof-of-concept investigation of pathogenesis of NMS using glutamate-based functional magnetic resonance imaging.

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Case Report

A 55-year-old man was admitted with a history of acute-onset high-grade fever, severe generalized tremors and an altered level of consciousness for the last 2 days. On admission, the patient had a pulse rate of 116 beats/min, blood pressure 140/80 mm Hg, temperature 103.4°F respiratory rate of 32/min, and oxygen saturation of 95% although inhaling room air. The patient was being treated for bipolar disorder for the last year. He was on risperidone (30 mg/day), clonazepam (0.5 mg/day) and olanzapine (7.5 mg/day). Neurological examination revealed Glasgow coma score 12/15, disorientation, lead-pipe rigidity, brisk jerks, and coarse tremors. Examination of the other systems was normal.

The patient's treatment was initiated with cooling blankets, intravenous infusion of acetaminophen, and lorazepam. Routine investigations of blood revealed elevated erythrocyte sedimentation rate (100 mm 1st h), raised serum creatinine (1.5 mg/dl), and a very high creatine phosphokinase level (3522 Units/dl). His electrocardiogram and chest X-ray were normal. Bacterial and fungal cultures of blood were negative.

Magnetic resonance imaging of the brain was obtained with a 1.5T scanner (General Electric, USA). T2 sequences showed mild hyperintensities in basal ganglia bilaterally [Figure 1a]. Simultaneously, magnetic resonance spectroscopy was carried out with single [inner green box in Figure 1b] and multi-voxel regions [outer white box in Figure 1b] of interest. The regions of interest (ROI) were specified manually. Figure 1c shows

a similar image at a different level. Figure 1d shows the presence of increased levels of glutamate in the single-voxel ROI (625 mm^2) (arrowhead) with relaxation time (TR) 4200 and excitation time TE 103.8. A heat map of the glutamate concentration was generated [Figure 1b and c], which showed increased levels of glutamate in both the basal ganglia.

The contribution of each hemisphere to the clinical scenario was analysed by parallel-beam radon transformation analysis of the heat map generated by magnetic resonance. This was carried out using the image analysis toolbox of MATLAB (MATLAB 2008a, MA, USA). The result showed marked symmetry [Figure 2], confirming equal participation of both hemispheres.

Discussion

The potential of HMRS to assess concentration of neurotransmitters in specific ROIs have opened up avenues of patient monitoring in dementia and other psychiatric diseases. NMS can be considered as a scenario where well-known pathways of glutamate excitotoxicity are greatly exaggerated. However, there is little objective evidence of this knowledge in the literature. Although the incidence of NMS is lower than conditions like Alzheimer's disease, this was the rationale for selection of the patient.

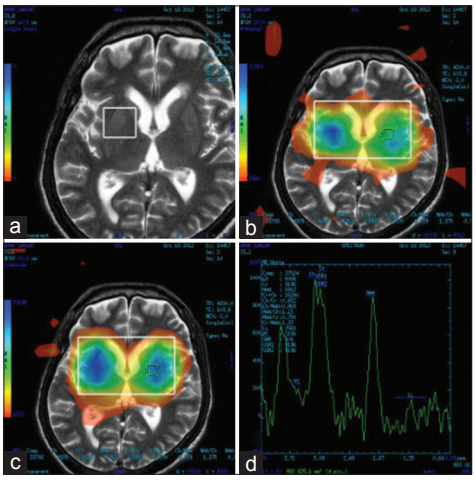

Figure 1: HMRS study of brain. (a) T2 sequence showed hyperintensities in both basal ganglia. (b, c) Showed concentrations of glutamate by multivoxel imaging (TR 4200 TE 103.8). The inner green square identified a single voxel. (d) Magnetic resonance spectroscopy curve showed elevated glutamate levels (arrowhead)

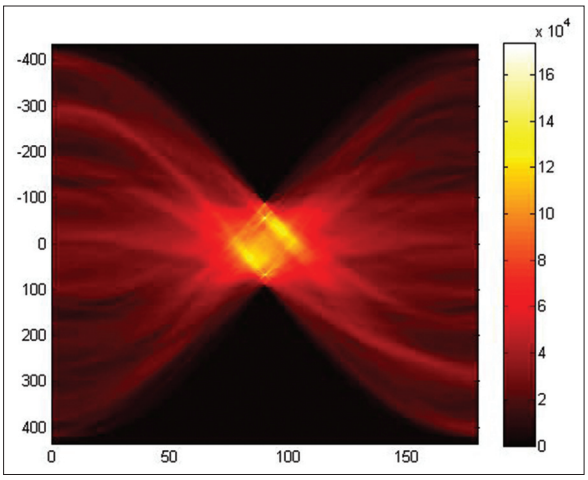

Figure 2: Radon transformation of the glutamate concentrations in the multi-voxel regions of interest in Figure 1. This revealed a bilaterally symmetric involvement of basal ganglia

Multi-voxel imaging has been shown to correlate with clinical severity of autism.[5] Therefore, a single voxel HMRS was carried out initially to prove the excess of glutamate, followed by a multi-voxel imaging to map the concentrations of glutamate. In our patient, the severity of the clinical features and laboratory values correlated with the heat map. However, larger studies that include suitable controls are necessary to comment on its usefulness as a clinical application.

Language function in humans are linked with inter-hemispheric asymmetry and is possibly a result of functional specialization.[6] In schizophrenia, there is decreased activation of cortico-cerebellar-thalamic circuit in the right hemisphere.[7] Although bilateral affection is biologically plausible in NMS, no evidence has emerged until date. I performed radon transformation of the image obtained by HMRS to clearly visualize the level of symmetry of glutamate levels in the basal ganglia. Radon transformation has been utilized to detect red blood cells in microscopic images.[8] Our report suggests that, it can have applications in detection of cerebral in homogeneities.

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