GABAergic Changes in ^{11}C-Flumazenil PET in the Drug-Naïve Stiff-Person Syndrome

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Stiff person syndrome (SPS) is a rare disorder of the central nervous system, characterized by fluctuating rigidity of the truncal and proximal limb muscles and spasms.[1] The pathophysiology of SPS remains elusive, but laboratory and functional neuroimaging studies suggest that γ-aminobutyric acid (GABA)ergic dysfunction plays a major role in its pathogenesis.[1-4] Positron emission tomography (PET) studies using the benzodiazepine antagonist ^{11}C-flumazenil (FMZ) showed significant reduction of FMZ binding in brains of patients with SPS, which implied the decrease of the postsynaptic $GABA_A$ receptor availability in the brains of SPS patients.[2-3] Magnetic resonance spectroscopy (MRS) demonstrated significant reduction of brain GABA levels in patients with SPS. MRS results suggested a correlation between reductions in GABA levels and SPS severity, but this was not investigated using ^{11}C-FMZ PET. We observed a correlation of laterality between reduction of FMZ binding, as shown by ^{11}C-FMZ PET, and clinical severity in a drug- naïve SPS patient.

Case Report

A 37-year-old woman visited Asan Medical Center due to discomfort in both legs, more predominantly on the right side. This discomfort had started ten months earlier with pain of the right hip accompanying lower back pain, and progressed to the right thigh and then to the right lower leg, combined with stiffness in right knee. Eight months after symptom onset, she could not perform daily tasks due to severe stiffness and pain in both legs. The symptoms were asymmetric, progressive and fluctuating. Anxiety and stress provoked more frequent spasms in both legs, as well as chest tightness. Her medical history was unremarkable. There was no history of autoimmune diseases, including type-1 diabetes mellitus, hyper- or hypothyroidism, pernicious anemia, or myasthenia gravis, or seizure disorders.
Neurological examination showed increased muscle rigidity of both legs, especially on the right side, with normal muscle strength. She could walk with much difficulty and limping. Sensory examination was normal. Deep tendon reflexes were normal active for her upper extremities and hyperactive for her lower extremities, but neither Babinski's sign nor Hoffman's sign was observed.

Laboratory tests, including serum glucose, hemoglobin A1c and thyroid function tests, were normal. No oligoclonal bands were detected and the immunoglobulin G (IgG) index was normal. The concentrations of anti-glutamic acid decarboxylase (anti-GAD) antibody were markedly increased, 83.4 U/ml in serum (normal range: 0-1 U/ml) and 77.5 U/ml in cerebrospinal fluid (CSF). The index for intrathecal synthesis of anti-GAD antibody (anti-GAD-specific IgG index)[1] was 235.4, strongly indicating intrathecal synthesis of IgG anti-GAD antibody. She was negative for paraneoplastic antibodies test, including anti-Hu, anti-Ri, anti-Yo, anti-CRMP5 and anti-amphiphysin antibodies, by indirect immunofluorescent stain with the triple tissue slide (mouse stomach, cerebellum and kidney).

Magnetic resonance imaging of her brain and spinal cord were normal. Nerve conduction studies were normal and electromyographic studies showed continuous motor unit action potentials at rest in her right leg muscles. Her motor evoked potentials were normal. Tests for malignancy, including chest computed tomography (CT), mammography, breast ultrasonography, abdominopelvic CT and pelvic ultrasonography, were all negative.

To assess $GABA_A$ receptor dysfunction, ^{11}C-FMZ PET was performed. The patient was injected with 15mCi of FMZ, and its accumulation was recorded for 60 minutes by dynamic serial scanning. Summated images of dynamic serial scanning from 40 to 60 minutes were used for analysis. Visual analysis showed decreased FMZ binding in the left motor cortex, which correlated with the asymmetry of the motor symptoms and signs (Figure). FMZ binding values were measured using ellipsoid shaped regions of interest (ROIs) and expressed as cortex to pons ratios. ROIs included the superior and inferior frontal, primary motor, superior and inferior parietal, insular, temporal, occipital and cerebellar cortices. An asymmetry index (AI) was calculated using the formula (right − left)/(right + left)/2. We found that FMZ binding values in the primary motor cortices were lower than in other cerebral cortical regions and that the AI was about three times higher in primary motor cortex than in other brain regions (Table).

The patient had been treated with intravenous immunoglobulin (IVIG) for five days, as well as baclofen, diazepam and clonazepam. Her stiffness gradually improved. She was given IVIG treatments at one-month-intervals for initial two months and at two-month-intervals thereafter. Her serum concentration of anti-GAD antibody gradually decreased to 77.6

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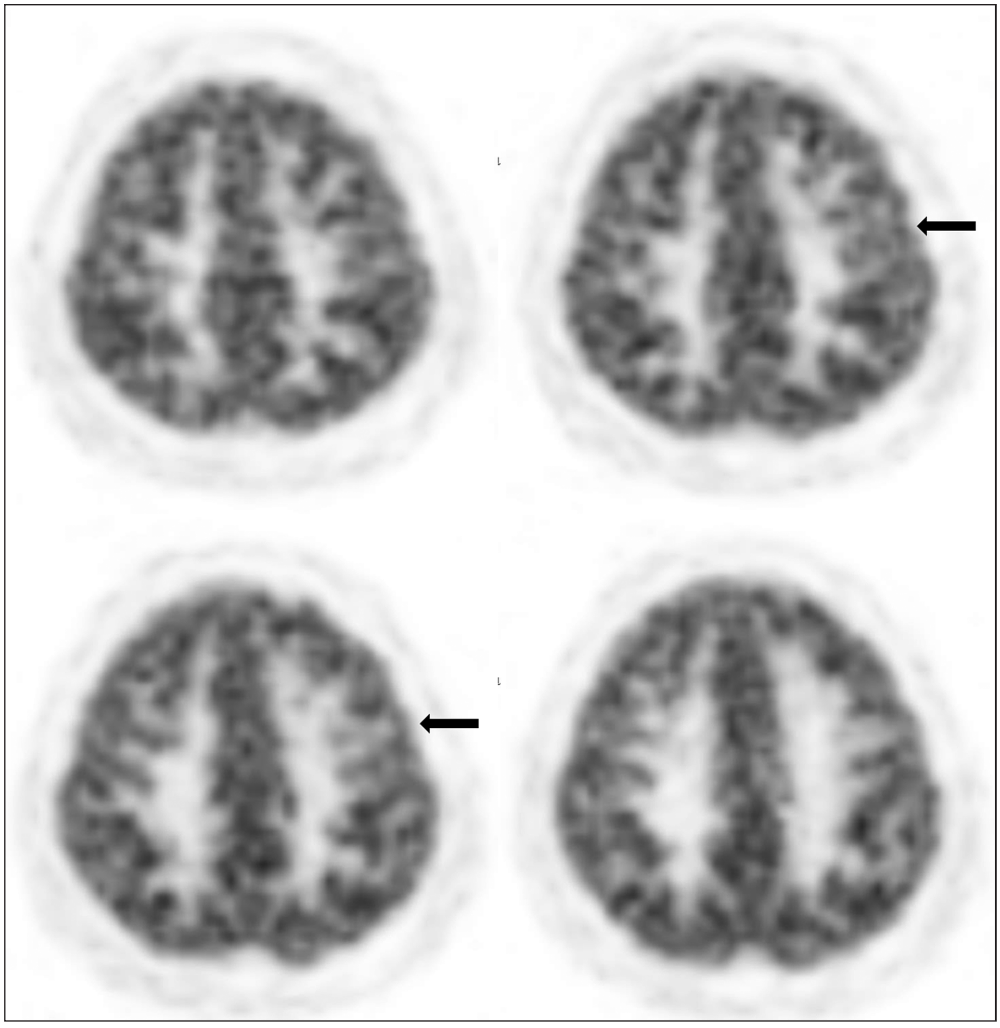

Figure: *^{11}C Flumazenil PET showing decreased binding potential in the left motor cortex (arrow)*

Table: Flumazenil binding value and asymmetry index in ^{11}C-flumazenil PET

	Left	Right	Asymmetry index*
Primary motor cortex	2.85	3.58	0.227
Superior frontal cortex	4.12	4.14	0.003
Inferior frontal cortex	4.27	4.61	0.098
Superior parietal cortex	3.90	3.97	0.081
Inferior parietal cortex	4.55	4.22	0.075
Insular cortex	4.29	4.68	0.087
Temporal cortex	4.35	4.38	0.007
Occipital cortex	4.68	5.17	0.099
Mean ± SD	4.13 ± 0.57	4.35 ± 0.49	0.085 ± 0.069

Flumazenil binding value was expressed as cortex to pons ratio; *Asymmetry index = (right − left)/(right + left)/2; SD, standard deviation

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U/ml (93.0% of initial level) at two months, 76.6 U/ml (91.8% of initial level) at three months.

Discussion

The ^{11}C-FMZ PET results in our patient suggest that reduction of FMZ binding may correlate with the clinical severity of SPS, even at the early stages. ^{11}C-FMZ, a benzodiazepine antagonist, binds mainly to $GABA_A$ receptors in the neocortex, with lower binding in the hippocampus, basal ganglia, thalamus and cerebellum,[5] and is commonly used in PET scans to measure cerebral $GABA_A$ receptors *in vivo* in humans. Reduced FMZ binding, coupled with normal MRI findings may indicate reduced $GABA_A$ receptor density on neuronal cell surfaces. Therefore, reduced FMZ binding was induced by postsynaptic GABAergic dysfunction, which might result in the disinhibition of neuronal activity with subsequent muscular stiffness.

The ^{11}C-FMZ PET findings in our patient suggest relatively decreased $GABA_A$ density in the motor cortex, indicating that the cerebral cortex may be the primary pathologic area in SPS. Moreover, decrease in FMZ binding were asymmetric in the two hemispheres, correlating with the asymmetry of our patient's clinical features. Although we did not show normalized ^{11}C-FMZ PET data using normal controls, clear asymmetric reduction of FMZ binding in our patient might suggest abnormal pathologic process occurred in the cerebral cortex of patients with the early, drug- naïve SPS. These findings were not reported in previous studies using ^{11}C-FMZ PET scan, perhaps because patients had symmetric symptoms and signs. Our patient had relatively moderate and asymmetric symptoms and had not taken any medication at the time of the PET scan. Most patients in previous studies had taken medications that may have affected ^{11}C-FMZ PET findings.[2-3]

A hypothetical mechanism for reduction of FMZ binding might be the autoimmunity to $GABA_A$-receptor-associated protein (GABARAP) in stiff-person syndrome. Recently, Raju et al suggested the possibilities that GABARAP may be an autoantigen of pathogenic significance in SPS, and in that study, a significant decrease was found in the level of GABARAP in patients with anti-GAD antibody positive SPS, and about 70% of the patients showed significantly high anti-GABARAP antibodies correlating with clinical severity.[6] The GABARAP are thought to be important for assembly and surface expression of $GABA_A$-receptor, so the dysfunction of GABARAP in SPS patients along with the effect of anti-GABARAP antibodies support the GABAergic impairment in the brain of patients with SPS. In our patient, anti-GAD antibodies were markedly increased both in serum and CSF with high anti-GAD-specific IgG index. GAD is a rate-limiting enzyme for the synthesis of GABA, the primary inhibitory neurotransmitter in the brain. Anti-GAD antibody is produced intrathecally and may impair the synthesis of GABA, resulting in low GABA levels in the brain and CSF.[1] Presumably, both presynaptic and postsynaptic GABAergic dysfunction might be possible mechanisms for the pathogenesis of SPS. Decrease of FMZ binding potentials in our patient support that SPS was possibly related to postsynaptic GABAergic dysfunction.

Conclusion

Decreased ^{11}C-FMZ binding potential in the patient with SPS may support that the primary pathologic substrates of this disease could be in the cerebral cortex. Moreover, the correlation between the clinical severity and ^{11}C-FMZ binding potentials suggest that ^{11}C-FMZ PET could be useful in evaluating the extent of brain involvement in patients with SPS.

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