

Disuse Left Hand Atrophy and Persistent Left Clenched Fist in an Adult with Catatonic Schizophrenia

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Abstract

Schizophrenia is a clinical brain syndrome with neuroanatomical, biological and molecular complexities. A wide range of aberrant motor functioning has been reported in 40-80% of patients with schizophrenia and some do overlap with patients' cognitive and negative symptoms.

Settings: A Department of Neurology and Psychiatry.

Case description: A 34-year-old male had schizophrenia characterized (in severe episodes) by apathy, negativism and auditory hallucinations. He had low intelligence (IQ = 68), schizoid personality traits and first degree relatives with schizophrenia. At the age of 27, he experienced stereotyped spitting behavior, bizarre facial grimacing and left persistent clenched fist posturing. Neurological evaluation revealed left hand posturing, atrophy and nail injuries of the hand flesh with fungal infection and motor apraxia. Therapy with different antipsychotics, electroconvulsive therapy and lorazepam resulted in partial clinical improvement but failed to improve hand posturing.

Assessment/Results: Transcranial magnetic stimulation (TMS) was delivered to M1 (right or left) using single-pulse paradigm. Cortical motor evoked potential (CMEP) was recorded from the contralateral abductor pollicis brevis (APB) muscle for determination of resting (rMT) and active (aMT) motor threshold stimulus intensities and cortical silent period (CSP) and from ipsilateral APB for determination of transcallosal inhibition (TCI or ipsilateral CSP). The results from stimulation of patient's right and left motor cortices were compared. They showed: (1) Lower rMT and aMT from right M1. (2) CMEP had similar latencies and amplitudes on both sides. (3) Shorter CSP from right M1, (4) Altered inter-hemispheric conduction times (TCI).

Discussion: We suggest the followings as possible pathophysiologic mechanisms of hand posturing: (1) Cortical disinhibition with hemispheric asymmetry (right > left), (2) Inter-hemispheric disconnection syndrome and motor apraxia. (3) Cognitive deficits with possible impaired cognitive control of movement, and (4) Neurodevelopmental deficits.

Keywords

Catatonia, Schizophrenia, Hand atrophy, Cortical disinhibition, Inter-hemispheric disconnectivity, Transcranial magnetic stimulation

Introduction

Schizophrenia is a clinical brain syndrome with neuroanatomical, biological and molecular complexities. There are substantial clinical variations

(heterogeneity) from patient to patient in the cognitive, emotional, perceptual and motor manifestations; therefore schizophrenia is not a specific disease. Because of this, the traditional subtypes of schizophrenia (e.g. paranoid, disorganized and undifferentiated) were dropped from Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) [1] as they are descriptive and not validated as entities or effective in reducing heterogeneity. DSM-5 suggests that each patient with schizophrenia requires designation of which particular pathologies are present and provides a list of at least 8 fundamental manifestations. These are delusions, hallucinations, motor, negative symptoms, cognition, thought disorganization, mania and depression. A wide range of aberrant motor functioning has been reported in 40-80% of patients with schizophrenia and do overlap with patients' cognitive and negative symptoms [2]. They include catatonia (5-32%) [3, 4], soft neurological signs (97-100%) [5], extrapyramidal manifestations (9-17%) [6], slow gross and fine motor activities and psychomotor retardation [4].

Catatonic syndrome is characterized by homogeneous positive and negative psychiatric (behavioral and affective) and motor features. Authors reported approximately 40 features of catatonia [3, 4]. Its commonest features are combination of negativism, posturing, grimacing and muscle stiffness (55-65%), while the uncommon features are waxy flexibility, stereotypy, echolalia/echopraxia, and verbigeration (35%) [3].

Review of the literature of antipsychotic naïve patients with evidence from experimental, clinical, postmortem and functional neuroimaging and neurophysiological studies support that intrinsic motor symptoms in schizophrenia are closely related to the followings: (1) Altered functions of the non-primary motor cortices [which are premotor cortex (area 6), supplementary motor area (SMA) and anterior cingulate cortex], posterior parietal cortex, basal ganglia, cerebellum, thalamus, and brain stem; (2) Altered inter- and intra-hemispheric, cortical-subcortical and short- and long- cortical connecting fibers and tracts [7-10]; (3) Disturbed metabolism of the thalami, frontal lobes and basal ganglia [11]; (4) Cognitive deficits with possible impaired cognitive control of movement. (5) Neurodevelopmental pathology [2]; and (6) Disturbed balance between inhibition (γ amino butyric acid or GABA)/excitation (glutamate) in local cortical networks, basal ganglia and cerebellum [12].

Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiological method which used to measure the neural conduction and processing time, activation thresholds, facilitation/inhibition in brain cortex (primary and non-primary motor areas), and neural connections. Review of the literature showed the use of the following single- and paired-pulses TMS paradigms to evaluate functions of motor and non-motor cortices in patients with schizophrenia [12, 13]: (1) resting (rMT) and active motor (aMT) thresholds, (2) cortical motor evoked potential (CMEP) latency and amplitude, (3) cortical silent period (CSP), (4) short- (SICI) and long- (LICI) intervals cortical inhibition, (5) I-wave facilitation, (6) intracortical facilitation (ICF), and (7) transcallosal inhibition (TCI) and facilitation (TCF). They found cortical

disinhibition, predominance of cortical hyperexcitability and intra- and inter-hemispheric disconnectivity [12, 13].

In some patients, treatment of catatonic manifestations with antipsychotics may be challenging because both negative and positive symptoms are present in the same patient at the same time and many studies reported worsening of catatonia with some antipsychotics due to dopaminergic blockade. Electroconvulsive therapy (ECT) is the treatment of choice for catatonic schizophrenia [14, 15]. Benzodiazepines have showed some clinical success in few patients (e.g. acute schizophrenia, short duration of catatonic symptoms prior to treatment, stuporous conditions, excitement, schizoaffective disorder, and absence of gross central nervous system abnormality prior to onset of schizophrenia) [3, 14-16]. Other treatment options for benzodiazepine resistant patients include: some atypical antipsychotics (e.g. risperidone, olanzapine, ziprasidone and aripiprazole) [3, 15].

Case Presentation

A 34-year-old male has the diagnosis of schizophrenia since adolescence. He had normal gross motor development and attended school till grade 6. The mother mentioned that he had lower intelligence compared to her healthy siblings. He works as a buffet worker. He gets married and has two children. He had schizoid traits and a strong family history of schizophrenia (a father, brother and first degree cousins). His psychiatric manifestations during severe episodes (twice per year) were psychomotor retardation, apathy, negativism, decreased appetite and poor self-hygiene and auditory hallucinations. At the age of 27, the mother noticed that he developed a continuous spitting behavior which was disgusting to others but his close relatives accepted his behavior as part of his illness; he showed bizarre facial movements only to people outside doors but did not show this behavior to people inside doors (e.g. protruding and retracting his tongue, elevating his eye brows and others); and he assumed left forced clenched fist posturing (for 90-100% hours of the day even during sleep). He had no previous history of alcohol or illegal drug abuse or head injury. He had no history of other neuropsychiatric, medical, physical or surgical problems. The diagnosis of schizophrenia with catatonic syndrome (negativism, stereotypy, facial grimacing and posturing) was assumed based on psychiatric interviewing and DSM-5 diagnostic criteria. Revision of patient's previous treatment regimens showed that he received ECT and different antipsychotics (e.g. risperidone, aripiprazole and olanzapine), mood stabilizers (e.g. carbamazepine) during severe relapses followed by maintenance oral antipsychotic medications (risperidone or olanzapine). The mother mentioned that despite the good improvement of his behavior, there was persistence of left hand posturing in the remission states. At presentation, his Bush-Francis catatonia rating scale score (BF CRS) was 21 [17], intelligence quotient (IQ) was 68 (assessed using Wechsler Adult Intelligence Scale version III (WAIS-III) [18]) and Mini Mental State Examination (MMSE) score was 16 [19] (normal reference value is 26.04 ± 1.9 [20]). Gross neurological evaluation revealed presence of poor speech fluency, unremarkable neurological and physical

examination apart of left hand posturing (force clenched fist), hand atrophy and nail injuries of the hand flesh with fungal infection. The patient was able to voluntarily unfold his hand but seemed apraxic (lack of response for instructions to flex, extend abduct or adduct his fingers) (figure 1). The examiner noticed that the patient was able to keep his fist unclenched for a period of time after instruction to unclench it but returned to its persistent posturing once lack of instruction to unclench it. There was absent palmar planter reflex. Notable improvement (BFCRS score was 6) was observed within three months after treatment with risperidone (3 mg/day), olanzapine (10 mg/day) and benztropine mesylate (2 mg tid). Follow-up of the patient (every 6 months) showed notable improvements of different catatonic features (negativism and grimacing, mild improvement of stereotyped spitting behavior on maintenance treatment with olanzapine (10 mg/day) but there was complete absence of use of the left hand. Trials with lorazepam in a dose of 3 mg/day for 6 months also failed to improve hand posture. His conventional magnetic resonance imaging (MRI) of the brain, electroencephalography (EEG) and blood chemistry were normal. Using single-pulse TMS delivered to M1 to the abductor pollicis brevis (APB) muscle, the following parameters were assessed (from the right and left hands): rMT, aMT, CMEP (latency and amplitude), CSP duration (TMS delivered to M1 to contralateral APB) and TCI (also called ipsilateral CSP or iSP, i.e. TMS delivered from M1 to ipsilateral APB muscle). Patient's results were as follows (Table 1): (1) Reduction of right rMT and aMT (MEP was recorded from left APB) compared to the left (indicating cortical disinhibition or predominance of cortical hyperexcitability). (2) CMEPs had similar latencies and amplitudes on both sides (indicating intact pyramidal tracts). (3) Reduction of CSP duration from the right M1 compared to the left (indicating cortical disinhibition and predominance of cortical hyperexcitability). (4) Altered inter-hemispheric conduction times (TCI) (indicating impaired transcallosal inhibition or inter-hemispheric disconnectivity).

Informed written consent was obtained from the patient and his mother to publish and discuss his data.

Discussion

We present a patient with catatonic schizophrenia. He had mixed negative and positive symptoms but the predominant manifestations which were troublesome to his family were his positive motor manifestations (stereotypy, facial grimacing and unilateral persistent left hand posturing). Based on the clinical, neurophysiological evaluation and his normal other medical and physical histories and examinations, the suggested possible pathophysiologic mechanisms of hand posturing may include the following: (1) Hemispheric asymmetry in cortical inhibition/excitation (cortical disinhibition) (as evidenced by reduced rMT, aMT and TCI), (2) inter-hemispheric disconnection syndrome with impaired motor praxis system (as evidenced by the difference in transcallosal inhibition despite normal latency and amplitude of CMEPs indicating normal corticospinal pathways), (3) Presence of cognitive deficits (as evidenced by low scores of MMSE) and impaired cognitive control of movement, and (4) Presence of neurodevelopmental deficits (as evidenced by low IQ) and possible re-activation of the primitive palmar grasp reflexes (disinhibition of cortical or corticospinal networks).

Although clenched fist posturing appeared as self-sustaining and the patient or the examiner were able to maintain it open for a period of time if the patient's hand (palm uppermost) was rested on his lap (Figure 1), however, its return to hand posturing most of the day and even during sleep and intact bilateral pyramidal tracts support the presence a significant focal structural or functional asymmetries [i.e. cortical inhibition/excitation or input to M1 (inter- and intra-hemispheric disconnectivity)]. Previous studies (using single-pulse or paired-pulse TMS stimulations) revealed that impairment of cortical inhibition (cortical disinhibition) and predominance of cortical hyperexcitability may underlie excessive motor overflow in patients with schizophrenia [12, 13]. Previous studies discovered considerable volumetric alteration in the brain asymmetry since childhood in patients with schizophrenia which involves the hippocampus, temporo-parietal region, basal ganglia and parts of the limbic system, regions with key roles in learning, motor control, emotions and higher-order executive functions [21]. TMS studies found that the most consistent replicated finding in patients with catatonic schizophrenia is persistent reduction of SICI throughout different stages of illness [12]. SICI is a

Table 1: TMS parameters results of the patient.

TMS parameters	Patient	
	Right M1	Left M1
MT stimulus intensities		
rMT; %	25	44
aMT; %	20	32
CMEP		
Latency; ms	18.6	18.2
Amplitude; mv	1.25	0.99
Duration; ms	35.5	30.7
CSP		
Duration; ms	65	110
TCI (iSP)		
Duration; ms	22	11

TMS was delivered to M1 to contralateral abductor pollicis brevis muscle (APB). For TCI, TMS was delivered to M1 to ipsilateral APB muscle.



Figure 1: (A) Forced left hand clenched fist (posturing or forced grasp), left hand atrophy and nail injuries of the hand flesh with fungal infection. (B) Similar findings of the left hand after 6 months treatment with lorazepam and olanzapine.

measure of inhibitory postsynaptic potentials (IPSPs) mediated by ionotropic GABA_A receptor [22]. Others reported increased ICF and I-wave facilitation [12] and reduced CSP and TCI (also called inter-hemispheric inhibition or IHI10). I-wave facilitation suggests deficient function of cortical inhibitory GABAergic activity. ICF and I-wave facilitation are measures of cortical excitation mediated by NMDA and non-NMDA glutamate receptors, respectively [23]. Reduced CSP duration indicate impaired GABAB-mediated cortical inhibition [12, 22]. Some reported increased CSP duration with clozapine but not with other antipsychotic therapies [24]. Experimental studies in mouse model of schizophrenia reported the beneficial effect of clozapine (which facilitated bindings of GABA to GABAB receptors [24, 25] and baclofen, a GABAB agonist [26] in normalization of cortical network behavior. Reduced IHI10 at rest or increased ipsilateral CSP duration (TCI) had been reported in patients with schizophrenia indicating impaired transcallosal inhibition [12]. In normal persons, using paired pulse stimulation elicits two periods of inhibition, (a) at intervals of ~10 ms (IHI10) and (b) at intervals of ~40 ms (ipsilateral CSP). Evidence from lesion studies suggests that IHI10 is mediated via the corpus callosum as people with callosal lesions have absent or reduced IHI [12]. In support, (a) studies using combined TMS and electroencephalography (EEG) found cortical oscillations deficiencies in both motor and non-motor areas in patients with schizophrenia, indicating excitation/inhibition imbalance. (b) studies discovered that abnormalities in glutamatergic transmission are strongly associated with abnormal brain asymmetry, loss of synaptic connectivity, and a schizophrenic behavioral pattern [27]. (c) Studies using combined TMS and functional MRI-brain showed widespread cortical-cortical and cortical-subcortical disconnection in patients with schizophrenia [9, 10, 28].

Neurological evaluation of this patient revealed that he was unable to control his left hand although he had intact corticospinal tracts indicating hemineglect and apraxia. This might be due to dysfunction of SMA, motor cingulate gyrus and failure of the frontal lobe to inhibit parietal lobe function. Studies in schizophrenia reported altered frontostriatal and frontoparietal inter-hemispheric disconnection and corpus callosum disconnection syndrome [9, 10].

For this patient, therapy with ECT, different combination of antipsychotic and use of lorazepam showed no notable improvement of hand posturing. In accordance, Ungvari et al. [29] did random assignment, double-blind, placebo-controlled cross-over trial with lorazepam (6 mg/day) for 18 patients with clinically stable chronic schizophrenia with enduring catatonic features. The authors kept the re-existing medication constant throughout the study. The authors did comprehensive assessment of the patient at baseline and four weekly intervals thereafter. However, they observed no effect for lorazepam on the patients' catatonic signs and symptoms. In contrast, Rosebush et al. [3] in their prospective open trial observed that the use of lorazepam in a dose of 1 to 2 mg was able to improve catatonic manifestations (immobility, staring, mutism, withdrawal, posturing, grimacing and rigidity) within 2 hours in 80% (12/15) of patient. Authors indicated that that the lack of improvement of catatonic manifestations with

lorazepam may occur in patients with chronic schizophrenia, longer duration of catatonic symptoms prior to treatment and presence of central nervous system abnormalities [14-16].

Although, the patient had absent palmar grasp reflex, however, the patient's hand position looks similar to the strong holding phase of the primitive grasp reflex due to maintained continued contraction of the flexor and adductor muscles of the fingers of any length. We suggest that the presence of neurodevelopmental deficits and re-activation of the primitive palmar reflexes (disinhibition of cortical or corticospinal networks) may be possible causes of persistent left hand posturing. The primitive palmar grasp reflex is a spinal cord reflex and is inhibited with maturation of the neural networks, particularly the frontal brain regions [medial or lateral frontal cortex anterior to M1 and non-primary motor areas, SMA, premotor cortex (area 6) and cingulate motor cortex] and integrity of prefrontal dedicated neural networks [2, 7, 10]. It reappears in some brain disease states [e.g. neurodegenerative diseases, a tumor or vascular lesion in a frontal lobe] or even in the absence of overt brain pathology.

In summary, we present a patient with catatonic schizophrenia. His predominant motor manifestations were stereotypy, facial grimacing and persistent left hand posturing. The possible pathophysiologic mechanisms of patient's hand posturing may include: asymmetric abnormalities between the two cerebral hemispheres in cortical inhibition/excitation; inter-hemispheric disconnection with motor apraxia, cognitive deficits with impaired cognitive control of movement and/or neurodevelopmental problems with re-activation of the primitive palmar grasp reflex.

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Conflict of Interest

The author declared no conflict of interests.

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