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The Distinctive Movement Disorder of Ovarian Teratoma-Associated Encephalitis

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Video 

Abstract: The movement disorder observed in four cases of ovarian teratoma associated encephalitis is described. The illness began with neuropsychiatric symptoms and was followed by prolonged unresponsiveness, respiratory failure, and autonomic instability. The movement disorder consisted of semirhythmic repetitive bulbar and limb movements and persisted during prolonged periods of unresponsiveness, diminishing as awareness returned. The characteristics of the movement disorder differed from recognized dyskinesias. It is suggested that interruption of forebrain corticostriatal inputs by anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies removes tonic inhibition of brainstem pattern generators releasing primitive patterns of bulbar and limb movement. Recognition of the distinctive movements should prompt a search for an ovarian teratoma since the condition is responsive to tumor resection and immunomodulation.

Key words: ovarian teratoma; encephalitis; dyskinesia

Ovarian teratoma-associated encephalitis (OTE) was first described in 1997[1,2] and recently found to be associated with NMDA receptor antibodies in serum and cerebrospinal fluid (CSF) that bind to rat hippocampus and the teratoma.[3] Case reports describe various involuntary movements associated with OTE. These are reviewed and discussed along with our experience of four further cases of OTE which suggests the movement disorder is complex and distinctive.

PATIENTS AND METHODS

Over the last decade we identified four patients who exhibited a distinctive and in our experience unique movement disorder in the setting of encephalitis with prolonged unresponsiveness. Similarities between these cases and recent reports of OTE[3] lead us to review cases 1 to 3 and diagnose ovarian teratoma retrospectively. All teratomas contained neural elements. The retrospective diagnosis did not allow NMDA receptor antibody testing in cases 1 to 3 but these antibodies were detected in Case 4. The presenting features, clinical course, MRI appearances, and ovarian pathology were consistent with previous descriptions of OTE.[3]

Case 1

A 36-year-old woman presented with a 4 day history of insomnia, auditory hallucinations, dramatic mood swings, and racing thoughts 1 week after suspected tonsillitis. Initial medical observations noted a low

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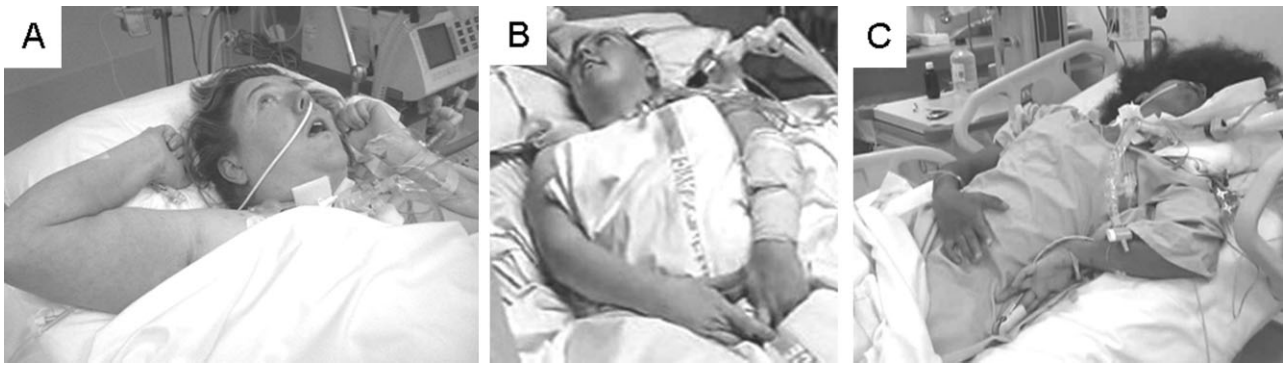

FIG. 1. (**A**): Case 1. A 36-year-old woman in a state of wakeful unresponsiveness, exhibiting tonic upward gaze deviation, with elevation of the eyebrows, mouth opening, neck extension and dystonic posturing of the upper limbs and hands, in conjunction with semi-rhythmic facial, neck and upper limb movements. (**B**): Case 2. A 22-year-old woman, exhibiting episodes of tonic hyperextension of the neck, tonic gaze deviation and dystonic posturing of the arms, hands and fingers. These postures occurred in the setting of semi-rhythmic movements during a state of wakeful unresponsiveness, accompanied by tachycardia, sweating, and hypertension. (**C**): Case 4. A 17-year-old woman, exhibiting tonic hyperextension of the neck and dystonic posturing of the upper limbs. The postures were superimposed on semi-rhythmic upper limb movements.

grade fever, stooped posture, decreased facial expression and continual 'chewing' movements. Speech output was reduced with suspicious and disorganized content. An acute psychosis was diagnosed and treated with olanzepine. Over several days she became less responsive, interspersed with periods of frenzied activity. Episodes of truncal hyperextension occurred. Olanzepine was ceased and benztropine administered without benefit. All investigations including brain magnetic resonance imaging (MRI) were normal.

She then became mute and akinetic with a divergent strabismus, rigidity, catalepsy and brisk tendon reflexes. Hypertension and tachycardia (150 bpm) were unresponsive to metoprolol. She was intubated. Extensive immunological and microbiological testing was unremarkable apart from a CSF pleocytosis (3 neutrophils, 55 lymphocytes). Treatment with prednisolone was commenced for immune encephalitis. Periods of unresponsive wakefulness alternated with coma for the next 2 weeks.

During this time a succession of abnormal movements developed. Rhythmic flexor posturing of the neck and trunk was followed by periods of tonic upgaze with extensor posturing. Complex patterns of repetitive facial movements appeared, with rolling and protrusion of the tongue (video 1), pouting and grimacing (video 1), jaw opening and closing (video 2), repetitive frowning (video 2), and bruxism. These movements had a variable frequency around 1 Hz. Sometimes the movements were synchronous with bilateral jerking of the upper limbs, which were held in unusual postures (video 3, Fig. 1a).

Electroencephalograms (EEG) showed no epileptiform activity. Hypersalivation and labile blood pressure were noted. Intravenous immunoglobulin (IVIG) was administered. Flexion responses to pain returned and grasp reflexes were elicited. One week later alertness improved, with semipurposeful saccades and exploratory upper limb movements. Responsiveness to environmental stimuli increased and she became extremely agitated. Assisted ventilation was weaned. Facial movements worsened when lorazepam was weaned. Comprehension and speech returned. Short term memory, insight, and verbal fluency were poor. The facial movements ceased. Mobility rapidly improved but limb rigidity, bradykinesia, and retropulsion persisted. Sleep inversion and rapid eye movement (REM) sleep behavior disorder were noted. She was transferred for rehabilitation and improvement continued.

Five months later she was functioning normally except for persistent lethargy and nocturnal behavior consistent with REM sleep behavior disorder. Examination demonstrated minor cognitive slowing, decreased verbal fluency, mild rigidity, and subtle bradykinesia. Computed tomography (CT) subsequently demonstrated a 5×9 cm^2 ovarian teratoma which was excised and found to contain neural elements.

Case 2

A 22-year-old female presented with confusion, agitation, insomnia, and visual and auditory hallucinations after a 2 week history of headache, rash, and nausea. Subsequently, involuntary tongue protrusion and chewing facial movements appeared.

Examination revealed rhythmic chewing movements, mouth opening, nares flaring, lip pouting, and bruxism. CSF revealed a pleocytosis (16 neutrophils and 24

lymphocytes/microliter) and elevated protein (0.64 g/L, normal range 0.10–0.60). Extensive microbiological and immunological studies were normal. Haloperidol and droperidol were given for agitation. Generalized rigidity, decreased responsiveness, and oxygen desaturation supervened requiring intubation. Brain MRI was normal.

Off sedation she was unresponsive to voice and pain. There were rhythmic (1.5 Hz) movements consisting of complex patterns of mouth opening, chewing, palatal elevation, and asymmetric grimacing (video 4). Synchronous eye movements were superimposed on tonic gaze deviation (video 4), these movements were also synchronous with flexion-extension and supination-pronation upper limb movements (video 4). Movements evolved spontaneously and were increased and modified by sensory stimulation (video 5). The limbs were rigid with dystonic hand posturing (Fig. 1b). Episodes of tonic gaze deviation with neck and trunk hyperextension were accompanied by tachycardia, sweating, and hypertension (video 5). Chewing movements caused facial trauma. Apnoeic periods alternated with hyperventilation. Hypersalivation required glycopyrrolate. EEG demonstrated no epileptiform features. This clinical state persisted for the ensuing 2 months.

After 3 months improvement allowed withdrawal of ventilatory support. Involuntary bulbar movements continued. Jerky semipurposeful limb movements appeared. Sleep inversion was noted as alertness increased. Over a period of several days she became less responsive, hyperthermic, rigid, dehydrated and hypernatremic, and was found in cardiorespiratory arrest, a decline reminiscent of 'malignant catatonia'.[4] The total duration of illness was 4 1/2 months. Autopsy demonstrated a small, mature ovarian teratoma. No neuronal loss was evident at brain autopsy and only a sparse diffuse supratentorial perivenular and leptomeningeal inflammatory infiltrate was found.

Case 3

A 21-year-old female presented with a 1 week history of polydipsia, insomnia, anorexia, emotional lability, agitation, auditory hallucinations and delusions, preceded by headaches and constipation. Fluctuating periods of altered awareness and catalepsy followed. Investigations were normal. Psychosis with catatonia was diagnosed and treated with electroconvulsive therapy and neuroleptics. Her conscious state declined and generalized rigidity developed.

She became febrile, tachycardic, hypertensive, tachypneic, and salivated excessively. Her eyes opened only to deep painful stimuli. She was intubated. Semirhythmic facial movements were noted (elevation of the eyebrows, flaring of the nares, chewing, and platysma contraction). A divergent squint developed with periods of tonic upgaze and truncal hyperextension.

Extensive testing for causes of encephalopathy was negative. Brain MRI was normal. EEG demonstrated generalized slowing. CSF contained 3 neutrophils, 5 lymphocytes, normal protein, and unmatched oligoclonal bands.

Presumed immune encephalitis was treated with prednisolone. Within days she became more alert, intermittently following commands with purposeful limb and eye movements. Sleep-wake cycle was disturbed with sleep reversal and sleep cycle prolongation. The bulbar movements diminished. Several weeks later speech, then mobility and continence returned. Short term memory, insight, and verbal fluency were poor. Prednisolone was tapered. Four months later a mild short-term memory deficit, poor insight, decreased verbal fluency, micrographia, and decreased arm swing were evident. She eventually returned to normal. A CT scan performed 3 years later revealed a 2×3 cm^2 left ovarian teratoma with neural elements demonstrated histopathologically.

Case 4

A 17-year-old woman presented with a 2 week history of fever, headache, muscle aching, and 1 day of confusion. She then became agitated and paranoid with severe short term memory impairment. Brain MRI was normal. EEG showed diffuse delta wave activity. CSF contained 480 lymphocytes, 1 neutrophil/microliter, and elevated protein (1.01 g/L (normal range 0.10–0.65)). Limbic encephalitis was diagnosed. Seven days after admission she developed respiratory failure and was intubated. A pelvic ultrasound demonstrated a 1 cm right ovarian mass. A teratoma with neural elements was excised.

Rhythmic (0.5–1 Hz) mouth movements then developed with grimacing and tongue protrusion, sometimes associated with elevation of the eyes (video 6). At other times mouth movements were synchronous with complex movements of the upper limbs with internal rotation of the shoulders, elbow flexion and spreading of the fingers (video 7, Fig. 1c), superimposed on dystonic posturing of the arms and hands. Another variation was rhythmical smiling, with eye opening and elevation of the eyebrows, not always in phase (video 8).

The rhythmical tongue protrusion became asynchronous with jaw opening, causing tongue trauma. Asymmetrical hand patting movements were also seen. All movements increased when she was stimulated and were refractory to sedative drugs. Anti-NMDA receptor antibodies were detected by Professor Josep Dalmau (University of Pennsylvania). Despite high dose methylprednisolone, IVIG, and rituximab she has not yet improved 3 months later, except for some diminution of her movement disorder.

DISCUSSION

Four cases of OTE are described in whom a nonspecific prodrome was followed by neuropsychiatric symptoms, prolonged periods of unresponsiveness, autonomic instability, and central respiratory failure accompanied by a distinctive movement disorder. The movement disorder comprised repetitive semirhythmic ocular, jaw, facial, lingual, limb and trunk movements, with oculogyric deviation, opisthotonus, and dystonic limb posturing. The bulbar movements consisted of mouth opening and closing, bruxism, chewing, facial grimacing, frowning, lip pouting, and tongue protrusion. Limb movements ranged from an undulating motion to jerking and sustained posturing. The movements appeared synchronous at times and independent at others. The pattern of movement was variably influenced by sensory stimulation even though the movements occurred during depressed consciousness. The movements resolved as responsiveness returned.

Abnormal movements with a predilection for the mouth and face are described in many case reports of OTE. Although it is difficult to assert they are identical without video comparison, the similarities to our cases are striking. The movements have been described as 'chewing,'[5,6] 'continuous jaw opening,'[7] 'grimacing,'[6,8] 'tongue thrusting,'[6] 'twitching,'[3,5] 'orofacial dyskinesias,'[7,8] 'involuntary,'[3,9] partial seizures,[3] and epilepsia partialis continua.[3,9] It is unclear whether all reported 'seizures' are epileptic since electroencephalographic detection of ictal activity is uncommon and the rhythmic movements with tonic eye deviation may be misinterpreted as epileptic.[3,7] Other movements are also described including tremor, dystonic, choreoathetoid, myoclonic and ballistic movements, trunkal hyperextension, opisthotonic posturing, tonic gaze deviation, oculogyric crises, and rhythmic abdominal contraction.[3,5]

The continuous semirhythmic bulbar movements differ from other recognized orofacial dyskinesias. The movements did not have the random flow of chorea or spontaneous and tardive orobuccolingual dyskinesias. They were slower and more widespread than the 3 to 6 Hz upper lip and jaw tremor of the "rabbit syndrome."[10] Unlike most dyskinesias, the movements persisted during unresponsiveness, to the point of self-injury. Oculomasticatory myorhythmia in Whipple's disease[11] and extended palatal tremor[12] persist during sleep but movements in the present cases were more variable and widespread. Moreover, the characteristic ocular movements in these conditions were not evident.

Similar movements in unresponsive states are frequently discussed at movement disorder video sessions and attributed to "encephalitis," "brainstem encephalitis," "rhombencephalitis" or "encephalitis lethargica." Examples are also found in the literature. Blunt et al.[13] reported 2 cases of "encephalitis lethargica" presenting with altered behavior, psychosis, agitation, catatonia, and fluctuating consciousness. Case 1 exhibited chewing movements, oculogyric crises with opisthotonus, limb rigidity and dystonic posturing of the feet. The second case developed coma, respiratory failure, autonomic instability, grasp reflexes, rigidity, dystonic posturing of the limbs and grimacing, 'rabbit like' mouth movements with tongue protrusion followed by "dyskinesias" of the face, jaw, and tongue. The accompanying video of this case shows movements identical to those in the present report. Shill and Stacy[14] reported a 22-year-old female with 'malignant catatonia' due to 'encephalitis lethargica' who exhibited repetitive tongue thrusting, rigidity, tremor, catalepsy, dystonic posturing of arms and a mental state that fluctuated from agitation to mutism. Raghav et al.[15] described three young women, two of whom died, with an identical neuropsychiatric presentation followed by fluctuating conscious states, "rabbit-like oro-labial movements" (Cases 1,3), repetitive oculogyric movements (Cases 1,2,3) trunkal spasms and limb posturing (Cases 1,2,3), diagnosed as "encephalitis lethargica." Neuropsychiatric symptoms and movement disorders are prominent in encephalitis lethargica and OTE. Howard and Lees emphasized the importance of oculogyric crises, obsessive compulsive behavior, akinetic mutism, central respiratory irregularities and somnolence or sleep inversion as diagnostic criteria for encephalitis lethargica.[16] The characteristic movement disorder of OTE may be a useful distinguishing feature between the two conditions. In addition, the potential for recovery in OTE without residual post encephalitic parkinsonism, recurrent oculogyric crises and persisting neuropsychiatric or behavioral problems in most cases further suggests the illnesses are different.

The correlation between clinical course and antibody titer levels suggests the NMDA receptor antibodies in

OTE are pathogenic.[3] Interestingly, many features of OTE are identical to those induced by licit or illicit NMDA receptor antagonists. In phencyclidine ('Angel dust') intoxication hypertension, altered conscious states and bizarre or psychotic behavior are common.[17] Rigidity, focal dystonia, oculogyric crises, opisthotonic posturing, coarse tremor and twitching, facial grimacing, circumoral facial twitching, lip smacking, and chewing are also recorded. Catecholamine mediated hypertension and tachycardia,[18] amnesia, dysphoria,[19] and hypersalivation[20] are effects of ketamine anesthesia in humans. Abnormal breathing patterns,[21] rigidity,[21,22] and chewing movements[21] have also been noted with ketamine administration in animals and a ketamine-induced animal model of tardive dyskinesia has been developed.[23]

Reversible, antibody-mediated blockade of glutamate receptors is an attractive and parsimonious unifying hypothesis to explain the clinical features of OTE and the paucity of neuronal loss on cerebral pathology. NMDA receptor antibodies have varying specificity for receptor subtypes.[3] Pure amnestic forms of OTE may have more restricted binding to NR2A-containing receptor subtypes which are preferentially expressed in the hippocampus.[24] Antibodies that bind to the ubiquitous NR2B-containing subtypes[24] may produce a more severe and global phenotype.

The clinical features of catatonia, mutism, rigidity, catalepsy, grasp reflexes, dystonia, and profound neuropsychiatric disturbance at the onset and during recovery indicate a frontostriatal syndrome. Oculogyric and ocular motor disturbances and disruption of the sleep wake cycle point to basal ganglia and mesencephalic-diencephalic involvement. The complex organization of the ocular, bulbar and generalized trunk and limb movements implicates a rostral central pattern generator (such as the mesencephalic locomotor region) rather than one or both cerebral hemispheres. Brainstem central pattern generators are unlikely to be targeted directly by pathogenic NMDA receptor antibodies as these receptor subtypes are not found in the brainstem.[24] However, brainstem pattern generators are under tonic supratentorial GABAergic inhibitory control.[25] Diffuse supratentorial NMDA receptor silencing may reduce corticostriatal input and as a consequence reduce pallidal-mesencephalic tonic inhibition thereby releasing brainstem pattern generators from inhibitory control. Brainstem pattern generators are thought to drive rhythmic motion by conveying signals via reticulospinal projections to spinal neuronal networks in vertebrates from fish to man. Accordingly, the combination of semirhythmic bulbar and limb movements in OTE might represent release of primitive movement synergies including undulatory gill breathing and fin motion seen in fish and rudimentary chewing movements. In this respect, the patterns of facial and jaw movements were reminiscent of oral and masticatory automatisms observed in complex partial seizures and sleep parasomnias that appear when the stream of normal consciousness is suspended for any length of time (as was the case in OTE). Although disconnected from descending inhibitory control, brainstem pattern generators and their target neurons would still receive modulatory sensory afferent input, accounting for the variability of movements and the capacity of external stimuli to modify the movements. This model could also explain the diminution of movements with benzodiazepines[26] as well as the correlation between level of consciousness and movement severity.

LEGENDS TO THE VIDEO

Video Segment 1. (0:00–0:14) Case 1 Semi-rhythmic chewing, oro-facial (peri-oral and peri-ocular) and tongue movements are evident.

Video Segment 2. (0:14–0:35) Case 1 The movements changed in character to mouth opening, frowning and eye closure. Hypersalivation is also seen.

Video Segment 3. (0:35–0:57) Case 1 The bulbar movements were at times accompanied by semi-rhythmic upper limb movements and tonic gaze deviation (upwards in this segment).

Video Segment 4. (0:57–1:17) Case 2 exhibits semi-rhythmic movements of the jaw, face, neck and limbs. These movements were accompanied by tonic gaze deviation (to the left in this segment) upon which synchronous jerking of the eyes was superimposed.

Video Segment 5. (1:17–2:11) Case 2 This segment demonstrates the changing character of the movements in response to passive movement of the neck. Mouth opening and chewing movements variably change to pouting and eye elevation, grimacing, mouth opening with repetitive tongue movements. The semi-rhythmic nature, dystonic posturing and tonic gaze deviation persist throughout. These movements occurred in the setting of unresponsive wakefulness.

Video Segment 6. (2:11–2:22) Case 4 exhibits semi-rhythmic mouth opening and grimacing movements with eye closure and elevation of the eyes and eyebrows.

Video Segment 7. (2:22–2:38) Case 4 The facial movements were at times accompanied by slow, semi-rhythmic posturing of the limbs.

Video Segment 8. (2:38–2:56) Case 4 Facial movements were at times asynchronous, as this segment demonstrates, with semi-rhythmic smiling, eye opening and closure, variable tongue movements and eyebrow elevation.

Early view video: Videos 3, 4 and 7 are included.

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