The Neurodiagnostic Journal

ISSN: 2164-6821 (Print) 2375-8627 (Online) Journal homepage: http://www.tandfonline.com/loi/utnj20

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To cite this article: Eli S. Neiman, Spozhmy Panezai M.D., Sumaiya Salim M.D., Michael Seyffert M.D., Lazer E. Leifer MS IV, Michael Rosenberg M.D. & Sudhansu Chokroverty M.D. (2015) Bulbar and Limb Myorhythmia with "Smooch Sign": A Distinctive Movement Disorder in an Adult Patient with Reversible Anti-NMDA Receptor Encephalitis Associated with an Ovarian Teratoma, The Neurodiagnostic Journal, 55:3, 149-156, DOI: 10.1080/21646821.2015.1073069

To link to this article: http://dx.doi.org/10.1080/21646821.2015.1073069

The Neurodiagnostic Journal, 55: 149–156, 2015

ISSN: 2164-6821 print / 2375-8627 online
DOI: 10.1080/21646821.2015.1073069

Bulbar and Limb Myorhythmia with "Smooch Sign": A Distinctive Movement Disorder in an Adult Patient with Reversible Anti-NMDA Receptor Encephalitis Associated with an Ovarian Teratoma

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ABSTRACT. *Anti-N-Methyl-D-Aspartate receptor encephalitis is a recently described entity (Dalmau et al. 2007, 2008) that may present with a variety of complex movements in addition to other features (Kleinig et al. 2008). The purpose of our presentation of such a patient is twofold: (1) to characterize these complex oculo-oro-linguo-masticatory and limb movements with "smooch sign" as myorhythmia, based on a combined clinical and electrophysiological analysis (Masucci et al. 1984); and (2) to document possibly characteristic EEG evolution in the course of observation in our institution for three weeks from diffuse slowing to evolving rhythmic delta activity, which may represent a pattern of electrographic seizure activity.*

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Received: April 27, 2015. Accepted for publication: July 13, 2015.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/utnj.

KEY WORDS. *Anti-NMDA receptor encephalitis, dysautonomia, myorhythmia, paraneoplastic syndrome secondary to ovarian teratoma, slow wave status epilepticus.*

THE CASE

A 25-year-old woman with no significant past medical history or recent travel presented to an outside hospital with a seven-day history of headache, metallic taste in her mouth, myalgias, abdominal pain, nausea, and "bizarre behavior". She was irritable and had a low-grade fever upon admission, and evaluation for her fever and GI symptoms was initiated. Soon after, she became acutely agitated and confused, and a psychiatry consult was called for her disruptive behavior. With this mental status change and low-grade fever, the outside neurologists were concerned about the possibility of bacterial or viral meningitis/encephalitis and she was started on ceftriaxone, ampicillin, and acyclovir. Lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) tests showed a protein of 61 mg/dl, normal glucose, and 111 white blood cells (WBCs) with 98% lymphocytes. Magnetic resonance imaging (MRI) of the brain with and without gadolinium revealed subtle increased signal changes seen on fluid attenuated inversion recovery (FLAIR) series in the left limbic regions with no enhancement. Despite antibiotic and antiviral treatment she continued to deteriorate, becoming increasingly lethargic. She developed abnormal complex movements 8 days after admission, which were thought to be seizures, requiring intubation for airway protection and initiation of antiepileptic drugs (AEDs). Outside EEG showed a continuous slow wave pattern, per report, and the movements persisted. On day 12 of hospitalization she was transferred to our medical center, where she was noted to have a fever of 102ºF and sinus tachycardia (120–200 beats per minute). On initial examination off propofol, she was comatose, with eyes open and bilateral eye blinking and twitching but unresponsive to any vocal or mild noxious stimuli. She displayed complex semirhythmic movements involving both cranially and spinally innervated muscles. Most of the movements were semirhythmic or occasionally rhythmic and jerk-like (myoclonic) and would wax and wane. Repetitive ocular, oral, facial, jaw, lingual, and limb movements continued throughout the day, which could be suppressed only with propofol infusion. Mouth opening and closing (kissing) with chewing-like movements resembling bruxism, facial grimacing, and rhythmic flexion, extension, or opposition movements of the fingers were prominently seen (see video in Supplemental Material).

Clinically, the oculo-oro-linguo-masticatory movements appeared to be myorhythmia. These movements were not stimulus sensitive. The patient did not have palatal tremor (myoclonus). Extended and continuous EEG recordings were obtained early in her care, but, again, no epileptiform abnormality was seen with any of the above clinical findings. The continuous delta wave pattern was concerning for possible slow wave status, so several anticonvulsants were tried with no significant EEG changes.

She had brisk reflexes throughout, with indefinite plantar reflexes. Autonomic hyperreflexia ("autonomic storm") was seen with diaphoresis, hyperthermia, hypersalivation, and tachycardia, with heart rates in the 120–200 beats per minute range (see channel of EKG monitoring on EEG, shown in Figure 2 below), which required constant cooling, suctioning, and cardiac management.

Upon presentation, routine laboratory studies were performed on the patient's serum, including a vasculitis workup and heavy metals screening, all of which were unrevealing. Cultures of blood and sputum (including influenza A & B cultures) were negative, as were rapid plasma reagin, human immunodeficiency virus, Lyme, and fast treponemal assay studies. Thyroid studies were normal, as was antiperoxidase Ab. Urinary analysis showed a mild urinary tract infection and the toxicology screen was unremarkable. Three subsequent brain MRI studies were unremarkable for any pathology. Computed tomography (CT) of the chest showed bilateral lower lobe atelectasis with a right pleural effusion. With the above complex movements resembling automasticatory myorhythmia, she was evaluated for Whipple disease with central nervous system involvement. Biopsy of the distal duodenum and proximal jejunum showed no histological evidence for the disease, and a CSF study for *T. Whipplei* DNA polymerase chain reaction (PCR) was also negative. A CSF examination again showed elevated protein (72 mg/dl), normal glucose, and 265 WBCs with 98% mononuclear cells. Spinal fluid was again sent for gram stain, bacterial, fungal, and viral cultures and PCR testing, including herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, listeria, West Nile virus ribonucleic acid, and Eastern Equine virus IgG/IgM, with all studies negative. Cytology performed on the CSF was negative. Immunological studies were performed on serum and CSF for anti-Hu, anti-Ma 1& 2, antibodies to voltage-gated potassium channels, CV2/CRMP5 IgG antineuronal antibody, and anti-N-Methyl-D-Aspartate (NMDA) receptor antibody. Her anti-NMDA receptor antibody came back positive.

The patient had received several weeks of steroid treatment and six plasmapheresis treatments with no change in her clinical condition. She had a chest, abdomen, and pelvis CT and transabdominal and transvaginal ultrasounds, which were all unremarkable, with no teratoma or lesion found. The patient was transferred to a specialized cancer center where, due to her clinical presentation, including young age, abrupt onset of neuropsychiatric symptoms, severe dysatonomia, respiratory failure requiring intubation, coma, early flair changes seen on MRI in limbic regions of the brain, diffuse EEG slowing in the delta frequencies and likely electrographic seizures, stereotyped complex movements, positive anti-NMDA receptor antibody, and no response to antibiotics, antivirals, plasmaphoresis or steroids, after a global workup, she was taken to surgery. She was referred for surgery because of the strong evidence in the literature of the association between anti-NMDA receptor antibody-mediated and ovarian teratoma and due to the very high mortality rate for this paraneoplastic syndrome (Dalmau et al. 2008, Kirkpatrick et al. 2011, Vitaliani et al. 2005, Seki et al. 2008, Gable et al. 2012). Biopsy of her right ovary revealed a 9 mm ovarian

teratoma. Following surgery, she made remarkable progress and woke from her coma shortly after surgical resection, though had cognitive deficits per an outside report. Approximately 10 weeks post-surgery she was readmitted to the brain trauma unit (BTU) at our hospital, where she received several weeks cognitive and physical therapy. A repeat EEG during the readmission revealed a normal wake and drowsy recording with a 9 Hz well-formed posterior dominant rhythm. Approximately 1 year after discharge from our BTU, I called the patient to get permission to publish this manuscript and video recording. Her speech during our lengthy conversation was fluent, clear, and eloquent, with no dysarthria, aphasia, or word finding. When asked if she had any lingering neurological deficits she stated that she only has some occasional mild word-finding difficulties when overtired.

ELECTROPHYSIOLOGIC ANALYSIS

To characterize these abnormal movements, we performed surface electromyographic (EMG) recordings from frontalis, masseter, orbicularis oris, genioglossus, laryngeal, extensor digitorum communis, flexor carpi radialis, and tibialis anterior muscles. Semirhythmic (variable interburst duration) muscle bursts at a frequency of 1–1.5 Hz (average of 1.4 Hz) and a duration of 300–600 milliseconds (average of 400) were seen synchronously in all cranially and spinally innervated muscles (Figure 1). A minimum of 50 jerks were averaged. The triggering mode was an amplitude EMG threshold using a band-pass filter of 150–5 kHz for the EMG signal. The EEG filtering band-pass was set at 0.2–5 kHz. Low-frequency filter of 0.2 Hz is close to direct current recording for obtaining Bereitschaftspotential (Chokroverty et al. 1992, 2013, Shibasaki and Hallett, 2006) . The period of analysis ranged from -1000 to plus 1000 milliseconds relative to the onset of the muscle jerk. Back-averaging was obtained by using left orbicularis oris EMG as the trigger and averaging EEG beginning 1500 ms before EMG trigger. There was no EEG–EMG correlate (i.e., no cortical prepotential or readiness potential was seen).

Throughout her stay in the intensive care unit multiple extended and continuous EEG (cEEG) recordings were performed, revealing mostly severe generalized and fairly continuous delta/theta slowing at 2.5–4 Hz frequency with no well-formed posterior to anterior gradient (Figure2). Due to the EEG rhythmicity, synchronicity, and epochs of focal evolution, we were also concerned about the possibility of rhythmic delta as manifestation of status epilepticus in this patient with anti-NMDA receptor antibody-associated encephalitis (Kirkpatrick et al. 2011). During the cEEG monitoring we also later saw some evolving rhythmic bursts of 2–2.5 Hz delta waves seen intermittently lasting for 20 to 50 seconds without accompanying spikes or sharp waves, arising out of a diffusely slow background rhythm (Figure 3). Burst suppression pattern was seen in many recordings after propofol was started, with underlying delta activity with 2 to 3 seconds of electrical decrement seen between slow wave activity. No correlation was seen with complex myorhythmic and sometimes myoclonic

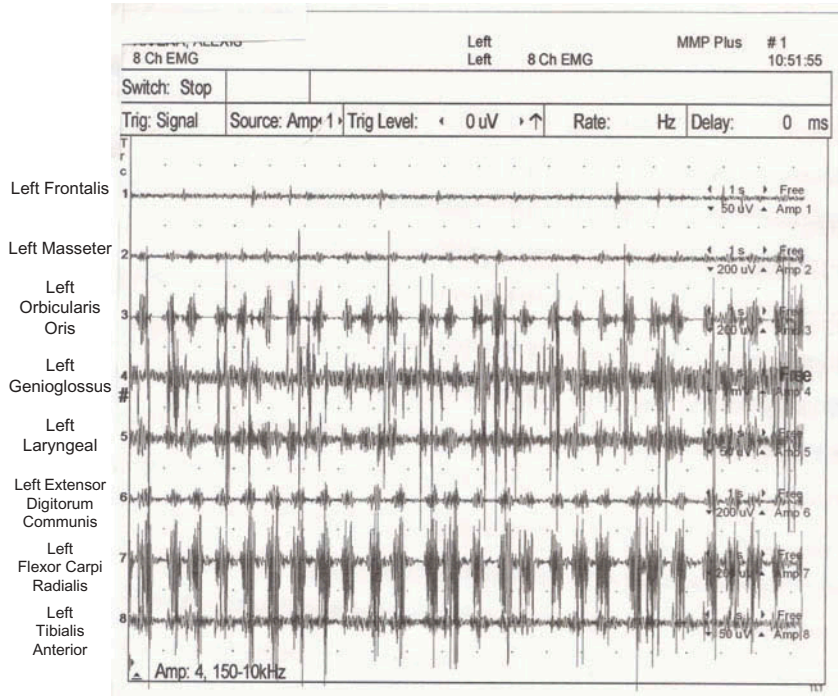

FIG. 1. Semirhythmic (variable interburst duration) muscle bursts at a frequency of 1–1.5 Hz (average of 1.4 Hz) and a duration of 300–600 milliseconds (average of 400) were seen synchronously in all cranially and spinally innervated muscles. Back-averaging was obtained by using left orbicularis oris EMG as the trigger and averaging EEG beginning 1500 milliseconds before EMG trigger.

movements and the EEG recordings. The patient was continued on several anticonvulsants and anesthetic agents throughout her hospitalization for the possibility of slow wave status with no clinical change seen (Kirkpatrick et al. 2011). Her AED dosing was increased, which did stop some of the rhythmic slow wave activity with occasional evolution, but the patient remained comatose.

DISCUSSION

Encephalitis is a relatively rare phenomenon, with most etiologies being caused by an underlying viral illness. Historically, about 37–50% of cases have had an unknown etiology. In 2007, Dalmau, Tuzun, and colleagues described encephalitis caused by an antibody against the NMDA receptor, and there have been over 500 cases reported in the literature since. Recent U.S. and international studies have found that this is the most common cause of encephalitis for individuals under 30 years of age and that the

FIG. 2. EEG recorded in our comatose patient with eye blinks and continuous rhythmic monomorphic delta activity with no clear posterior to anterior gradient. On channel of EKG monitoring on this digital page shows a heart rate of 180 beats per minute.

cause of 40–60% of those with anti-NMDA receptor antibody is ovarian teratoma. The median age of symptom onset is 21 years old, approximately 80–90% of cases occur in females, and paraneoplastic ovarian teratomas are most frequently found to be the underlying cause of this entity (Dalmau et al. 2008, Gable et al. 2012). Mortality rates for patients with anti-NMDA receptor antibody-mediated encephalitis is as high as 25% and relapse can occur in 20% of cases (Dalmau et al. 2007, 2008).

Our patient presented with most of the characteristic features of paraneoplastic anti-NMDA receptor encephalitis as recorded in the literature. These can be listed as follows: psychiatric symptoms of bizarre behavior and confusion (Vitaliani et al. 2005); complex movements (as described above); dysautonomia manifested by tachycardia, hyperhidrosis, hyperthermia, and hypersalivation (Vitaliani et al. 2005); altered state of alertness; distinctive EEG with possible evolution; cerebrospinal fluid showing mild lymphocytic pleocytosis with elevated protein but normal glucose; MRI flair signal changes in the limbic region (Seki et al. 2008); and often remarkable improvement following resection of an ovarian teratoma.

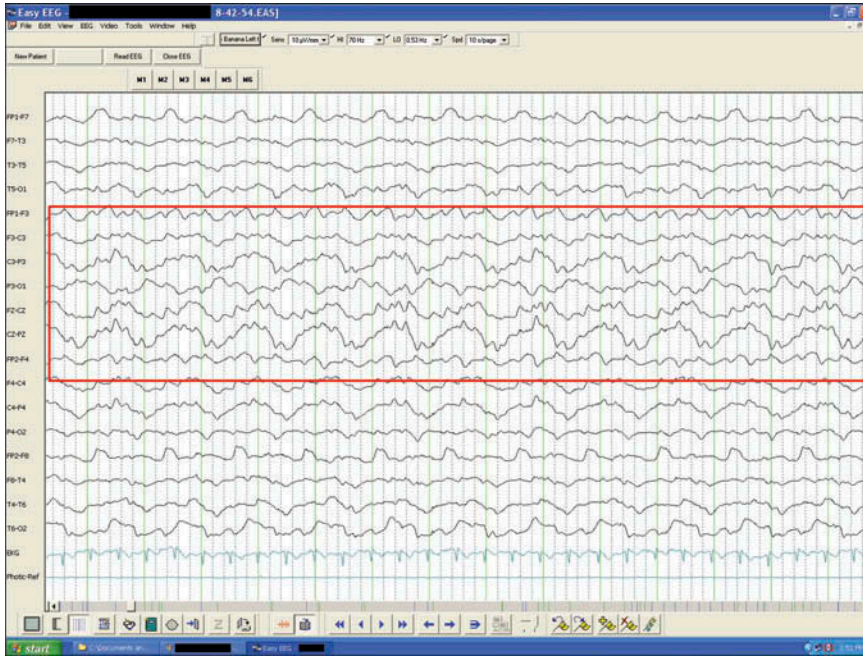

FIG. 3. Rhythmic 2–2.5 hz delta activity with a high amplitude focal seizure (evolution) seen in the left frontal, left parasagittal, and midline head regions.

The complex semirhythmic movements resemble myorhythmia based on an analysis of clinical and electrophysiological observations. The term *myorhythmia* was introduced by Herz in 1943 (and later clarified by Masucci et al. in 1984) to describe a rhythmic muscle burst at about 1.5–3 Hz which resembles rhythmic segmental myoclonus. The term palatal myoclonus was recently changed to palatal tremor because of rhythmicity. The term myorhythmia best describes this patient's movements because of the distinct rhythmicity occurring at a slow rate of 2–3 Hz. Although this resembles rhythmic myoclonus, the latter is often mixed with sudden arrhythmic myoclonic bursts. "Kissing" mouth movements, which we will designate as "smooch sign," seem to be a distinctive feature of this entity. These movements are slower (1–2 Hz) than the 3–6 Hz lip and jaw tremors of the "rabbit syndrome" of tardive dyskinesia seen after antipsychotic medications. The semirhythmic movements of our patient lacked the distinctive writhing and twisting components of classic athetosis or dystonia. Furthermore, most of this patient's movements lacked the feature of myoclonus (muscle jerks) or chorea (continual flow of movements from one body part to the other).

In agreement with the suggestion by Kleinig et al.(2008), these complex myorhythmic movements of anti-NMDA receptor encephalitis in our patient may have been driven by mesencephalic and pontine central locomotor pattern generators consequent to their release from descending cortical inhibitory input.

A high index of suspicion based on the above clinical presentation combined with electrophysiological characterization of complex movements and distinctive rhythmic EEG slow wave activity with or without evolution (extreme delta brush type pattern as described by Schmitt et al. 2012) that is very refractory to anticonvulsant treatment should raise the suspicion for paraneoplastic anti-NMDA receptor antibody encephalitis so that appropriate steps are taken for diagnosis and treatment.

SUPPLEMENTAL MATERIAL

Supplemental material for this article can be accessed at www.tandfonline.com/utnj.

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