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Clinical Reasoning: A Young Adult with New Seizures and Chapeau de Gendarme

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Abstract
Evaluation of new seizures is a common clinical query for neurologists. It can be challenging to delineate between the numerous etiologies of new focal or generalized seizures, and if focal, to localize their onset. In this case, we present a 26-year-old with a new onset of stereotyped events concerning for seizures featuring facial grimacing, dystonic left-hand posturing, and convulsions with immediate return to baseline. Throughout the case, we highlight a stepwise diagnostic approach to the evaluation of new onset seizures, discuss clues that seizure semiology can provide for localization of ictal onset, and review a novel and atypical presentation of a disease entity frequently encountered by neurologists.

Section 1:

A 26-year-old right-handed woman with no past medical history presented to an outside hospital for new recurrent stereotyped events concerning for seizures starting two days prior. She was in her normal state of health with no viral prodrome or recent travel. She had no family history of seizures or personal risk factors for epilepsy. She had two events at home, described by witnesses as "loss of consciousness" with "rhythmic, full body shaking." She was admitted to an outside hospital where she had normal vital signs, electrolytes and glucose and a negative urine toxicology screen. She was started on levetiracetam twice daily (30mg/kg per day). During the outside hospitalization, she had 5 more events described by their staff as left head turn and gaze deviation followed by full body shaking. She retained awareness during the events and immediately returned to baseline. Her levetiracetam was increased to 2g twice daily (60 mg/kg per day) given ongoing events. Her first lumbar puncture was performed 7 days after symptom onset. The CSF had 3 white blood cells (WBC; normal range <6 x10^6/L), 1 red blood cell (RBC), normal protein and glucose, negative meningitis panel, and negative rapid herpes simplex virus testing. She was transferred to our institution nine days after her initial presentation for continuous video EEG monitoring.

1. What is your differential diagnosis?

2. What further testing would you obtain?

Section 2:

Initial differential included seizure and psychogenic non-epileptic events (PNEE). Levetiracetam was reduced to 1g twice daily to help elicit events for diagnostic purposes on video-EEG. Scalp EEG demonstrated a normal background and sleep architecture with no interictal epileptiform abnormalities, but sixteen ictal events were captured including electrographic correlate. The event semiology featured either a sudden facial expression change in the form of a brief frown or pout (Figure 1), dystonic left hand and arm posturing, or both**.** The patient reported retained awareness during most of the events, and many occurred without a post-ictal state. Some of the events progressed to versive left head turn, left gaze deviation, left facial twitching, left lower extremity extension followed by clonic movements of the left hemibody. Two seizures progressed from focal to bilateral tonic-clonic.

1. How does this information change your differential diagnosis?

2. How would you localize this described seizure semiology?

3. What are your next diagnostic steps?

Our differential for new-onset focal seizures included structural etiologies, such as focal cortical dysplasia, heterotopia, and mesial temporal sclerosis; malignancy; autoimmune encephalitis; viral encephalitis; and idiopathic epilepsy. Given the rapid escalation of seizures without predisposing risk factors, there was high concern for a secondary etiology. Patient underwent MRI of the brain with 3 tesla epilepsy protocol which was normal. A second lumbar puncture was performed day 13 after seizure onset, with normal opening pressure and CSF studies including 4 WBC, 14 RBC, normal protein and glucose, negative herpes simplex virus and varicella zoster virus testing, normal IgG index, and no unique oligoclonal bands.

The seizure semiology lateralized to the right hemisphere given onset of left sided motor symptoms including left hand dystonic posturing. However, her EEG showed rhythmic theta most prominent over the left frontal polar region centered at F7/T7. She displayed a unique feature in many of her seizures called the "chapeau de gendarme" or "ictal pout," which is a finding seen in frontal lobe seizures, particularly in interhemispheric locations such as the cingulate gyrus.[1] Seizures such as this with interhemispheric onset can feature false lateralization on scalp EEG due to projection of the strongest signals from the medial surface to leads overlying the contralateral hemisphere. There is also connectivity within the frontal lobes that leads to rapid propagation of seizures which can further make localization challenging.[2] Additionally, retained awareness and lack of post-ictal state can be seen in frontal lobe seizures and may lead to the misdiagnosis of PNEE, though in this case, the stereotyped nature of events with a clear lateralizing semiology suggested against this.[3] To investigate further, distributed source localization was performed on an episode with the chapeau sign and demonstrated false lateralization due to an interhemispheric source of seizure onset located approximately in the right cingulate gyrus (Figure 2). Seizure onset was thought to be from either the cingulate gyrus region given the chapeau sign, or the right precentral premotor/supplementary motor regions given left hand and arm involvement. Most likely, multifocal seizure onset zones in these regions led to these two distinct semiology features.

At this time, the etiology for the new onset of seizures was thought to be idiopathic. Her levetiracetam was increased back to 1.5g twice daily, but she continued to have seizure clusters that required rescue benzodiazepines. Oxcarbazepine was added to her regimen, and she was seizure free for 24 hours prior to discharge.

However, five days after discharge, the patient developed frequent twitching of the left face and hand every two minutes, which did not respond to midazolam. She re-presented to a local hospital, where she developed auditory hallucinations of music as well as behavioral disinhibition and cognitive difficulties. Repeat MRI showed subtle T2 flair hyperintensities in

the bilateral temporal and medial frontal cortices. Levetiracetam was discontinued due to concern for exacerbating neurobehavioral symptoms, and her anti-seizure regimen was escalated over several days to include five medications.

Section 3:

1. Does this information change your differential?

The new psychiatric symptom of hallucinations, refractory seizures, and mesial temporal lobe hyperintensities increased the concern for autoimmune encephalitis. Autoimmune encephalitis panels sent from serum and CSF during prior admission returned positive for NMDA receptor antibodies.

Section 4:

1. What additional diagnostic steps would you undertake?

2. How would you treat this patient?

The patient next underwent a pelvic ultrasound which demonstrated an ovarian mass that was removed by gynecology and determined to be teratoma by pathology. She was treated with intravenous immunoglobulin (IVIG), steroids, and rituximab. Her seizures were better controlled with initiation of treatment, although she continued to have nocturnal seizures despite five anti-seizure medications. She was slated to receive additional rituximab in addition to monthly IVIG infusions.

Discussion

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a relatively common form of autoimmune encephalitis with an incidence of 1.5 per million per year.[4] It has a bimodal presentation, often occurring in young children and adults aged 20-40.[5] Its classic course is a viral prodrome, followed by psychiatric manifestations that may progress to seizures, movement disorders and eventually a comatose state. [6] However, anti-NMDAR encephalitis, especially in children, can present predominantly with seizures as demonstrated in our case.[7] It is still rare for patients to not have initial cognitive signs; however, they may be subtle, leading to diagnostic delays. [8] Only half of patients presenting with seizures have an abnormal MRI which suggests that normal initial diagnostic studies may not fully exclude autoimmune encephalitis as a cause of new seizures.[9] The CSF WBC is elevated in approximately half of anti-NMDAR encephalitis patients within 1 week of symptom onset and has been elevated in other case reports of anti-NMDAR encephalitis presenting with seizures.[10-11]

Multiple seizure types are described in anti-NMDAR encephalitis. Two-thirds of patients initially have convulsive seizures and there remains a slight predominance of these throughout the illness course [9, 12-13] However, 47-79% develop focal seizures and most have both types.[5,9,12] Status epilepticus (SE) is also relatively common with 30-40% developing it during their clinical course and it becomes refractory in approximately 21% of cases.[5,9,12] Despite the commonality of seizures in anti-NMDAR encephalitis, only half of patients have interictal discharges which may be due to deeper and highly localized epileptogenic zones.[14] The most common EEG pattern is

"slowing," typically in frontotemporal regions.[5,15] Extreme delta brush (EBD) is one EEG pattern strongly associated with anti-NMDAR encephalitis, although it is only found in about 30% of patients with seizures, and may be associated with a prolonged hospital course.[13] Patients with EBD often have normal MRIs and, in general, slowing on EEG is more common than abnormal MRIs which suggests EEG is important in early diagnosis[7,15]

The case we present is unique because the patient presented with seizures without initial cognitive features and with a unique seizure type. Her seizures exhibited the characteristic "chapeau de gendarme" or ictal pout which is a feature that helps localize seizures to mesial frontal regions, in particular the cingulate gyrus.[1] Although limbic encephalitis is typically thought to be a temporal lobe mediated process, frontal lobe seizures are described in anti-NMDAR encephalitis and it is important to keep anti-NMDAR encephalitis on the differential in these cases.[13] Our patient's particular seizure semiology, however, has never been directly attributed to anti-NMDAR encephalitis. Seizure localization on scalp EEG can be particularly challenging in seizures with an interhemispheric onset, and it is important to use semiology clues to guide localization.[2]

Overall, our case highlights an atypical presentation of anti-NMDAR encephalitis and the importance of maintaining it on the differential for new onset seizures even with initial normal diagnostics. Additionally, we demonstrate the unique "ictal pout" characteristic of mesial frontal lobe seizures and suggest this may be a clue for early seizure localization.

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Figure 1: Chapeau de gendarme sign during a focal seizure. A. Origin of the French phrase chapeau de gendarme, alluding to the shape of the hat worn by French police and military during the reign of Napoleon the 1st (upper panel: 'Napoleon Crossing the Alps' from wikipedia.org), see solid line shape contour below. **B**. Video screenshots linked with thick black lines to the scalp EEG recording shown below (L>R, anterior>posterior, maximal at F7, T7). The frowned mouth shape (chapeau de gendarme sign) is demonstrated in the first several seconds of the seizure.

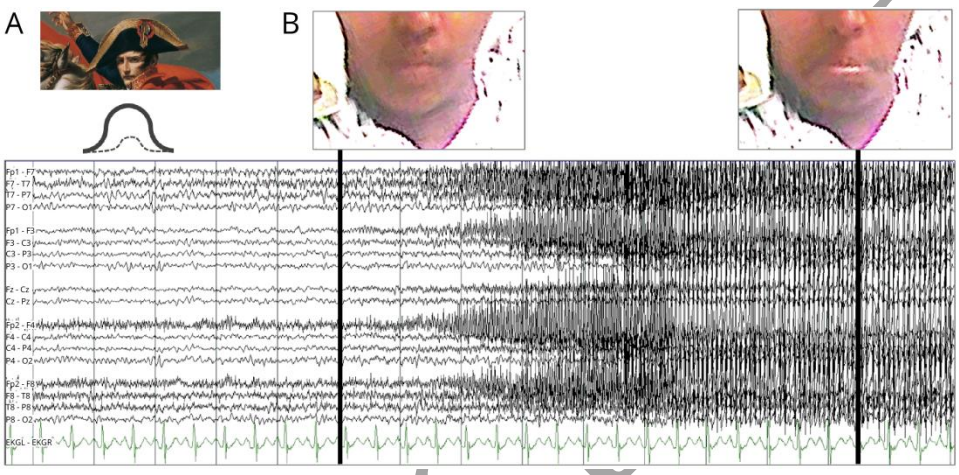
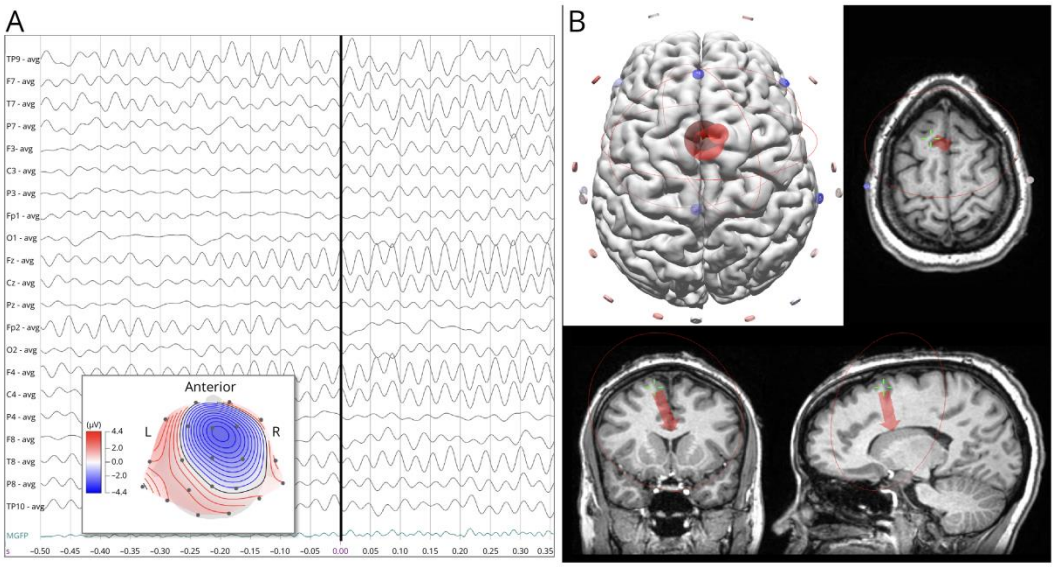


Figure 2. Electrical source imaging (ESI) for detailed localization of a representative seizure featuring chapeau de gendarme. A. Early focal ictal waves (common average montage, filtered between 3-40 Hz) are shown. In the lower panel, The EEG waveforms at the timepoint of the black vertical line are converted to a 2-D voltage map of the the scalp EEG-derived electrical field displayed from a top-of-the-head perspective. The negative polarity of the ictal wave source is shifted slightly to the right of midline. **B**. The ESI-modeled dipole of the data in A displayed in 3D (upper left) and on multiplanar MRI slices. The best fit of the ictal source maps to the medial frontal region approximately at the right anterior cingulate cortex.



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