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Topic: **NEUROLOGIC MYSTERIES: WHAT I’VE LEARNED AS A ROOKIE “DETECTIVE”**

Speaker: Maulik Shah, MD, Assistant Professor of Neurology, UCSF

Maulik Shah, MD, MHS is Assistant Clinical Professor of Neurology at UCSF. After undergraduate work at Stanford, he received his MD at Yale University, and then completed residency training in neurology at UCSF. He also completed his fellowship in the Neurohospitalist program at UCSF. His clinical focus is the management of patients with acute neurologic illness (including seizure disorders, auto-immune and inflammatory disorders, and infections of the nervous system) and how to best optimize work-flow efficiency and improve patient outcomes in the inpatient setting. He is involved in an ongoing collaborative effort to quickly and reliably identify patients at high risk for delirium in the hospital and working to prevent its onset and associated complications. He is also hoping to study abnormalities of complex neural networks underlying delirium using functional neuroimaging methods. In addition, He is involved in the education of neurology residents and medical students.

**Bibliography:**


What I’ve Learned as a Rookie “Detective”

Maulik Shah, MD, MHS
UCSF Neurology Department
Neurohospitalist Division

Outline
- Tools for the Neurology Detective
  - History-Taking and the Neurologic Examination
  - Mastery of Neuroanatomy
  - Diagnostic Testing
  - The Extant Literature
- Case Files: “Solved Mysteries”
  - Application of Tools in Making A Diagnosis
  - Learning from Previous Cases: Pattern Recognition
  - Avoiding Bias in Diagnostic Practice
  - Discussion of Pathophysiology

The Clinical Interview
- A proper history and description of patient’s symptoms remains the most important tool in neurologic diagnosis
- If the patient is unable to provide a history, it is vitally important to get collateral information from patient’s family members, bystanders, and other physicians or care providers
  - “What was the first symptom?”
  - “What was the tempo of onset of symptoms (abrupt and sudden versus slowly progressive)?”
- Past Medical History including Medications
- Social History and Exposures / Family History

The Clinical Interview, cont.
- Potential barriers
  - Language
  - Reliably of patient as historian: confusion, confabulation
  - Futility of language to describe certain symptoms
- Examples
  - “Dizziness” versus “vertigo” / cultural differences
  - “I feel weak throughout my body”
  - The experience of headache and pain: “What I have is not a migraine.”
The Clinical Interview, cont.

- The seasoned neurologist is able to ask focused questions to help clarify patient’s experience and to ask about subtle symptoms
- “Can you feel the tissue paper when you clean yourself on the toilet?” → saddle anesthesia
- “Can you tell the difference between cold and hot water?” → temperature sensation impairment
- “Do you have problems with combing your hair? Sitting up from a chair? Reaching up for cereal box?” → proximal muscle weakness

The Neurologic Examination

- The foundation of clinical neurology: developed and refined throughout the history of medicine with goal of localizing the lesion
- Important to be systematic in organization but also flexible depending on patient’s symptoms
- Complements clinical interview and history, and of particular importance when the history is limited / completely unknown
- Allows for direct functional interrogation of the nervous system

The Neurologic Examination

- Mental Status
  - Abnormalities implicate dysfunction of the cerebral cortex
  - Alertness and orientation
  - Language: naming, comprehension, and repetition
  - Memory / Visuospatial / Apraxia / Neglect

The Neurologic Examination

- Cranial Nerves
  - Set of 12 nerve pairs with specific functions involving vision, eye movements, hearing, facial muscle function, and swallowing
  - Knowing about structural relationship of nerves and how they travel out of the skull to their targets helps with localizing pathology
The Neurologic Examination

- Motor Function
  - Assessment of neurologic weakness of specific muscle groups in the arms and legs
  - Pattern of weakness helps in localizing source of weakness within the neurologic axis
  - Myopathy: proximal > distal weakness
  - Neuromuscular junction: fluctuation with repeated testing / fatigue
  - Brain or Spinal Cord: extensors > flexors

- Sensory Examination
  - Different anatomic pathways for pain/temperature versus vibration/propiroception
  - Asymmetry / Sparing of the Face

- Reflex Examination
  - Complements motor and sensory examination in assessing location within nervous system of cause of weakness or numbness
  - Using reflex hammer to test for hyper- or hypo-activity

- Coordination
  - Helps assess function of the cerebellum which helps with coordination of motor planning
  - Pathology manifests as ataxia or dysmetria
  - Can affect limbs or trunk of body
  - Involuntary movements such as tremor
The Neurologic Examination

- Gait Evaluation
  - Assessment of patient’s ability to stand and walk (or not) including noticing posture and positioning of legs, stride length and speed, and balance
  - In context of other aspects of neurologic testing helps in understanding why patient is having a hard time walking
  - Important to evaluate especially in cerebellar pathology as examination may be normal when patient is sitting or lying in bed

Patterns of Findings

- Upper versus lower motor neuron disease
  - Upper: brain or spinal cord
    - Increased or spastic tone, brisk hyperactive reflexes, pyramidal pattern of weakness
  - Lower: nerve or root, muscle, NMJ
    - Flaccid or floppy tone, absent or decreased reflexes, loss of muscle mass and atrophy, fasciculations
  - Motor neuron disease can have both types of findings (ALS / Lou Gehrig’s Disease)

Patterns of Findings

- Spinal Cord
  - Bowel or bladder difficulties
  - Numbness over buttocks/groin
  - Sensory level

- Parkinsonism
  - Resting tremor, slowed movements, shuffling gait with stooped posture, limb rigidity, micrographia

Limitations of Neuro Examination

- Diseases are often rapidly (or slowing) evolving so have to be mindful of changes in examination over time
  - For example, acute upper motor neuron problems like stroke or spinal cord injury often have lower motor neuron pattern of injury
  - Variability in how examination is done and interpreted
  - Old versus new finding? Is every finding clinically relevant?
  - Multifocal processes → multiple abnormalities
  - Certain aspects are very subjective and difficult to study objectively (sensory evaluation)
Diagnostic Testing

- Brain Imaging
  - CT scan versus MRI scan
  - Cerebral Vessel Imaging: Angiogram of Arteries
- EMG/NCS
  - “Extension” of the neurologic examination
  - Type of peripheral nervous system injury and severity
- Lumbar puncture
  - Analysis of CSF fluid to rule out infection or inflammation
- EEG
  - Scalp electrode monitoring of electrophysiologic cerebral activity; important in evaluation of seizures
The Experience of Others...
- In the modern era of the Internet and global information sharing, we have the great advantage of being able to do research online
- Review articles that describe common and uncommon features of disease seen in 100s of patients
- Information and case reports about rare diseases
- Communication with experts around the world
- Knowing where to look and for what is still a skill that must be learned over time
- Filtering through too much information / data

Making the Diagnosis...
- A recent study by Dhand and colleagues studied and documented which “tools” experienced neurologists used in clinic to help with making diagnosis
- Three main domains: clinical (history and physical); laboratory and electrodiagnostics; neuroimaging
- Relevant weight of these domains depended on diagnosis, but heavily weighted in all cases to the clinical domain

Case #1: The Eagle-Eyed Bystander

Figure from Dhand et al., Neurology, Oct 2013; 81:1460-1466.
History and Examination

- 75 year old right-handed man with high blood pressure and diabetes, who suddenly fell to the ground in the middle of the crosswalk at 11:00 am
- He goes on a walk every day for one hour and his wife said he was normal with no complaints when she left for work in the morning
- In the ED at 11:45 am, he was awake but did not attempt to talk and did not follow commands. He had drooping of the right face and did not move his right arm or leg. His left side moved spontaneously and he seemed to only look at people on the left side of the room.

Neuro-Anatomic Localization

- Multiple neurologic deficits
  - Right sided face/arm/leg weakness and numbness → left motor and sensory cortex
  - Visual field problem on the right → left hemisphere
  - Inability to talk or follow commands: *Global aphasia* → left hemisphere (90% of the time in people who are right-handed) involving language centers

Clinical Diagnosis: Acute Stroke

- Sudden onset and classic symptoms for an acute stroke
  - Ischemic versus hemorrhagic
  - Urgent CT scan to rule out hemorrhagic (bleeding)
How do we treat this problem?

- Clinical diagnosis of left middle cerebral artery large vessel ischemic stroke
- Patient with severe neurologic deficits
- What can we do to prevent permanent neurologic injury?
  - IV tPA: systemic “clot busting” medication
    - Guidelines: must be within 4.5 hours of symptom onset
  - Catheter angiogram to allow for direct lysis or mechanical removal of clot

Creating a Timeline

- It was our job to try and create a timeline of when stroke occurred and how long deficits have been ongoing
- Wife was last person to see patient “normal”, at five hours prior to our evaluation in ED at 7:00 am
- But we know that stroke occurred sometime after that since he clearly went out for his walk after his wife left
- From wife: walk was the same route every day, a loop that lasts one hour
- We gave her location of where he was found and she was able to say that this was near the end of his walk
Creating a Timeline

- We then called police to ask what they had noticed at the scene where he was found down.
- They said that patient was non-verbal and weak when they arrived at scene.
- Told us that a bystander had called 911 and told them about patient falling to ground. And they had her phone number!
- Called bystander, who stated that she was on other side of the street, saw patient walking normally, and then suddenly slow down and collapse to ground in middle of crosswalk at 10:45 am at which time she called 911.

Creating a Timeline

- Based on the collateral information, we were confident that stroke onset was at 10:45 am, about one hour before patient was evaluated in ED, and so made decision to proceed with IV tPA treatment.
- Patient did not improve initially and so family was consented for interventional treatment with mechanical removal of clot.
Clinical Course

- The next day, patient was able to talk and follow simple commands
- Mild right-sided arm and leg weakness but antigravity and able to hold a pen and write
- Eventually discharged home with plan for outpatient rehabilitation

Stroke

- Second leading cause of death worldwide
- Along with trauma, leading cause of disability
- Risk factors: high blood pressure, diabetes, high cholesterol, tobacco use, and cardiac arrhythmia
- Ischemic: 80% of cases, hemorrhagic: 20%
- Acute treatments are few and time-limited
- Importance of public education and awareness
- Call 911 with any worrisome symptoms

FAST

- Face is uneven
- Arm is weak
- Speech is strange
- Time to call 911
Lessons from Case #1

- Clinical context and examination quickly point to diagnosis of stroke with imaging helping to confirm
  - This is a diagnosis that is taught and discussed very early in the career of every neurologist
  - Importance of creating a timeline of symptom onset using any collateral sources of information
    - Vital to making decision regarding treatment
    - “Wake up” stroke debate
  - Stroke is a neurologic emergency with limited acute treatments
  - FAST!

Case #2: The Sinister Reclining Armchair

History

- A middle-aged man came to ED after waking up from sleep and noticing that he could not lift up his left hand or fingers and was noticed to have “wrist drop”
- Had several beers night before and fell asleep on his recliner with left arm draped over side of the chair
- He reports tingling over the back of her hand
- Question: Did this patient have a stroke?
Differential Diagnosis

- Radial neuropathy \( \rightarrow \) compression of the radial nerve after prolonged pressure from armchair
- Stroke involving the “hand knob” part of the homunculus

Radial Neuropathy

- Weakness of wrist extension, finger extension, and thumb movement away from hand
- Weakness of brachioradialis muscle (flexion action)
- Can also have weakness of triceps muscle if compression near armpit
- Lower motor neuron signs: flaccid tone, dropped reflex
- Clinical context: compression of nerve
  - Crutches, handcuffs
  - Saturday night palsy

“Hand Knob” Stroke

“Hand Knob” Stroke
- Usually no sensory abnormality (separate sensory cortex); if involved deficit is circumferential
- Very strategic stroke → spares face/leg/proximal arm strength
- Weakness of extensors > flexors; may spare brachioradialis
- Slowed finger taps, pronator drift
- Acutely can have flaccid tone, dropped reflexes
- Stroke risk factors: cardiac arrhythmia, high blood pressure, diabetes, high cholesterol

Making A Diagnosis...
- Combination of history and clinical situation and physical examination
- Classic story for compression of radial nerve
- Examination showed symmetric finger taps, weakness of finger extension, wrist extension, brachioradialis, along with tingling over back of the hand
- Diagnosis: radial nerve palsy / no need for head imaging
- Treatment: wrist brace, physical therapy, tincture of time

Clinical Reasoning Based on Neuroanatomy
- Knowing relationship of structures and function of this structures help guide rational thinking of localization of problem
  - Homunculus versus peripheral nerve dermatome
- “Know the Neighborhood”: What symptoms/findings are present or absent along with patient’s chief complaint?
  - Helps with localizing lesion and thus diagnosis
    - In this case cerebral cortex versus peripheral nerve

Corollary to Case #2
- Middle-aged woman with high blood pressure noticed numbness and tingling over her right arm, trunk and back, and proximal leg after waking up
- Acute onset, did not improve for three days so came to hospital
- No involvement of the face, no weakness on examination, intact reflexes, circumferential pattern of numbness
My first thought was that this was due to problem in sensory pathways of spinal cord since facial sensation was spared
- BUT: why would this happen acutely? No neck pain or trauma...
- No other spinal cord symptoms: bowel or bladder dysfunction, no sensory level over trunk
- Motor and sensory pathways very close within spinal cord → “Neighborhood”
- Acute onset: should always think about stroke
Lessons from Case #2

- Knowing neuroanatomy and structural relationships within the brain, spinal cord, and peripheral nerves, helps guide localization of symptoms and targets neurologic examination
- “Neighborhood” signs
- Neurologic examination as way to distinguish between causes of a common symptom (e.g. wrist drop, limb numbness)
- Never forget clinical context and pay attention to signs/symptoms that are NOT present

Case #3: The Man Who Slowed Down

History

- Elderly man with multiple medical problems including severe gastric reflux disease causing erosive injury to esophagus and severe nausea and vomiting
- Admitted to hospital for surgery repair
- Returned one month later for follow-up and his surgeon noticed that he was unable to stop drooling in clinic and had been losing weight due to difficulty swallowing
- Referred to Neurology Clinic for evaluation

History and Examination

- His partner also noted that the patient was walking much slower than usual and took longer to eat his food and change positions from sitting or standing
- On examination, he had marked bradykinesia
  - Long time to initiate movement, to start an action or walk
  - Lack of facial expressions, decreased blink rate, slack-jawed appearance with drooling out of both sides of mouth
  - Stiffness and rigidity in his arms > legs
  - Handwriting showed micrographia
- Slow, deliberate steps; stooped posture; several steps to turn; hard time keeping his posture when tugged from behind
Examination was consistent with Parkinsonism. The constellation of findings includes:

- **Resting tremor with pill-rolling quality**
- **Rigidity of limbs**
- **Bradykinesia**
- **Postural instability**

Other associated signs/findings include decreased facial expression, micrographia, shuffling gait with stooped posture and retropulsion, decreased arm swing, en bloc turning, and festinating gait.

Patient and partner note that these symptoms were not there at all prior to surgery.

**Parkinsonism**

- Often due to Parkinson’s disease
- A neurodegenerative disorder of the motor planning networks of the brain thought to be related to decreased levels of the neurotransmitter *dopamine*
  - Structures known as the basal ganglia nuclei
  - Usually cognitive symptoms do not develop until many years after motor symptoms and tremor
  - Treated with dopamine-based medications
  - Also seen in other neurodegenerative conditions which share features with Parkinson’s disease
  - Dementia with Lewy Bodies, Progressive Supranuclear Palsy

**Secondary Parkinsonism**

- However, this pattern of findings/signs can also be seen in other conditions that mimic Parkinson’s disease
  - Side effect of medications that block dopamine activity
  - Anti-nausea medications and anti-psychotic medications
  - Infections that affect the basal ganglia, such as West Nile virus
  - Toxins that affect the basal ganglia such as carbon monoxide and certain synthetic recreational drugs
  - Metabolic disorders: copper, iron, calcium deposition in these structures

![Basal ganglia and related structures](http://en.wikipedia.org/wiki/File:Basal_Ganglia_and_Related_Structures.svg)
Case #3 Diagnosis
- Onset over few weeks was likely too fast for Parkinson's disease
- Review of medications revealed that patient had been taking Metoclopramide (an anti-emetic medication) 4-6 times a day, even when he was not nauseated
- This fit with timing of symptoms and he was diagnosed with secondary Parkinsonism due to medication as cause of his drooling, difficulty eating, and slowed movements
- All symptoms slowly improved after stopping medication

A Complementary Case
- 37 year old man who flew to San Francisco from Central America by family for evaluation of progressive tremor in both hands, slowed movements and difficulty walking, and twitching movements of his whole body which were becoming more and more frequent
- Associated with cognitive decline, language difficulty, memory disturbance and inability to work (previously a partner in law firm)
- No history of similar symptoms in his family

Examination
- Disoriented and only responded to questions with 1-2 words
- Parkinsonism including tremor, bradykinesia, rigidity in arms, and decreased facial expression along with gait disturbance
- Myoclonus: Periodic jerking movement of arms and trunk every 5-10 seconds

Laboratory Evaluation
- Young patient with Parkinsonism but in addition prominent cognitive decline and myoclonus
- Not consistent with Parkinson's disease
- Infections/inflammatory disorders, toxic exposures, or other atypical neurodegenerative conditions
- Ordered MRI Brain, lumbar puncture, and EEG to help gather additional information and distinguish between these categories
Diagnostic Testing

- MRI Brain: non-specific subtle changes in the white matter on both sides of the brain
- Lumbar Puncture for CSF analysis: 8 WBC (normal < 5), more than 10 oligoclonal bands (normal < 1), and elevated IgG index 1.6 (normal < 0.6)
  - Suggestive of chronic inflammatory condition of the central nervous system

Diagnosis

- EEG was read as showing “periodic very high voltage and amplitude discharges associated with myoclonic jerks”
  - This finding is pathognomonic for “subacute sclerosing panencephalitis” also called SSPE
  - A rare disorder of inflammation of the central nervous system due to latent measles infection
    - Usually a pediatric illness; prevented by vaccination
    - Patient had measles at age 16
  - Diagnosis confirmed by sending for anti-measles antibodies from CSF

SSPE

- Rare neurologic complication of measles infection, often onsets years after initial exposure due to reactivation of latent infection
- Progressive cognitive decline, movement disorder and myoclonus, and gait disturbance → untreated will progress to permanent coma, and treatments often not effective
- Our patient was treated with direct anti-inflammatory therapy into the fluid space around the brain and slowly improved over the next year, eventually returning home
  - Now able to walk on his own, talk in full sentences
Lessons from Case #3

- Patterns within the neurologic examination can help guide the differential diagnosis
- Parkinson's Disease versus other causes of Parkinsonism
- Use of laboratory testing to complement history and examination in order to further help distinguish between categories of disease
- Some test results are pathognomonic for certain diseases and can lead you directly to confirmatory testing

Case #4: The Missing Nerves

Clinical History

- Case that I heard about as a clinical fellow, presented to me by on-call resident, as part of teaching exercise...
- 70 year old man with one year of weight loss, progressive weakness and difficulty breathing, and more recently double vision and drooping eyelids, with symptoms particularly severe at night, and better in the morning
- The patient reported seeing two objects at once with closing of one eye leading to loss of one of the images → confirms neurologic process rather than ocular problem
- Resident described patient as having marked weakness of his arms and legs, barely lifting them off of the bed, as well as having “multiple cranial neuropathies” / injuries

Examination

- Described as having following cranial nerve abnormalities
- Impaired left-sided eye movements with eyelid droop → left oculomotor nerve
- Impaired right eye lateral movement → right abducens nerve
- Right > left facial droop → right and left facial nerve
- Slurred and soft speech → glossopharyngeal and vagus nerves
My Differential Diagnosis

- Summarized by resident as a patient with “multiple cranial neuropathies, weight loss, and generalized weakness” – and I ran with it!
- My chief concern was for a process within the subarachnoid space - the space through which all cranial nerves travel once they leave the brainstem and before they skull to their targets around the head
  - In this age group, this is often due to cancerous process or chronic infection infiltrating into the subarachnoid space and causing injury to cranial nerves
  - Started to discuss work-up including lumbar puncture to sample fluid in this space and to test of infection/cancer...

Framing Bias / Error

- Framing effect: “Where the same problem receives different responses depending on how it is described”
- The practice of medicine, which relies on the passage of information between providers, is susceptible to these types of biases and potentially errors because data is meant to be interpreted and is often selectively highlighted
- As a clinician, I have to aware of this phenomenon, and always remind myself to “take a step back” from every case I hear about and make sure I am not narrowing my thinking prematurely or missing other possible diagnoses

My Differential Diagnosis

- As I was continuing my discussion with residents and students about potential diagnosis and work-up plan, my clinical mentor pointed out that all the cranial nerves that were “affected” controlled the function of muscles only – whereas all the nerves that control functions such as skin sensation, hearing, vision, or taste were spared
- Why would these nerves be “missed” by a process coating the subarachnoid space?
- Thus, it would be more likely that the problem was in the muscles themselves or in the neuromuscular junction, where the nerves connect with muscles

Returning to Case...

- When considering this new interpretation of findings, the diagnosis became much more clear
- Disorders of the NMJ worsen over time and can fluctuate in severity from moment-to-moment, often worse at the end of the day
- They tend to affect the muscles that control eye movement in particular, and double vision and eyelid drooping often are the first symptom
- The most common disorder of the NMJ is myasthenia gravis
Myasthenia Gravis
- Auto-immune disorder in which antibodies form against receptors within the NMJ, inhibiting communication between nerves and muscles, leading to weakness
- Often starts with ocular and facial muscles and then can spread to other muscles throughout the body
- Dynamic process which helps explain fluctuating symptom
- In severe cases, can affect muscles control breathing and swallowing, and patients require mechanical ventilation

Recency Effect / Bias
- Recency effect: "People tend to remember things at the end of a list of information best"
- In medicine, can fall into the trap of assuming that future cases with similar symptoms are due to the same disease you recently saw in another patient
- The next week, I saw a patient with new double vision after waking up from heart transplant surgery
- Immediately thought about myasthenia gravis or other diseases of the NMJ
- BUT: have to remember clinical context and onset
  - This was much more acute and after major cardiac surgery—patient found to have small stroke within the brainstem affecting nucleus of nerves that control eye movement
Lessons from Case #4

- An important skill as a clinical educator and as part of healthcare team is the careful interpretation of patient information and history obtained from other providers.
- Have to be aware of biases and errors that can be associated with interpretation of data.
- Be mindful of those biases in your own practice and never forget clinical context and the clinical interview, knowing that the same symptom or even examination findings in two different patients does not implicate the same diagnosis in both.

Case #5: The Picture Worth a Thousand Diagnoses

Clinical History

- 35 year old man with immune deficiency due to HIV virus presented with several months of progressive symptoms including weakness of his right hand, difficulty “finding the right words” and communicating with his family, and more recently frequent involuntary rhythmic twitching of his left hand.
- On examination he had UMN pattern of weakness in his right arm > leg with spastic tone and brisk reflexes, frequent errors when asked to name objects, difficulty seeing objects in the right side of his visual world, and periods of continued shaking of his left hand concerning for focal seizure activity.
HIV Neurology

- Patients with HIV (and all forms of immune system dysfunction) are at high risk for infections that involve the nervous system including bacterial, viral, or fungal organisms.
- Are also at higher risk for cognitive disorders and problems with peripheral nervous system including myopathy and neuropathy.
- Important to consider broad differential diagnosis with diagnostic testing helping to narrow possibilities.

Diagnostic Testing

- CSF showed normal WBC with no signs of inflammation.
- EEG confirmed that patient was having frequent focal seizures arising from right motor cortex.
  - Seizures controlled with medications.

MRI Result

- "Multifocal plaque-like abnormalities that are limited to the white matter of the brain sparing the gray matter."
- Involving both hemispheres, but asymmetric.
- Areas do not enhance when patient given contrast via peripheral IV → no breakthrough of blood-brain barrier.
- Areas are not associated with local swelling or "mass effect."
Differential Diagnosis
- In a patient at risk for several different types of infection and neurologic injury, and with an examination suggestive of multifocal process involving the brain, MRI scan has helped significantly narrow diagnostic possibilities
- White matter lesions with mass effect: HIV-associated lymphoma versus toxoplasmosis versus bacterial or fungal abscess
- White matter lesions without mass effect: viral process such as HIV encephalitis versus progressive multifocal leukoencephalopathy related to JC virus

Progressive Multifocal Leukoencephalopathy
- Severe demyelinating disease of the brain caused by reactivation of the JC polyomavirus, occurs also exclusively in immunocompromised patients
- Progressive multifocal neurologic symptoms depending on location of lesions within the brain
- Diagnosed by finding evidence of JC virus in CSF sample; CSF usually non-inflammatory
- No specific treatment, focus is on reversing immunosuppression and anti-retrovirals for HIV

Lessons from Case #5
- Localization of neurologic examination can be multifocal especially in diffuse processes of the nervous system
- Diagnostic imaging can help narrow differential diagnosis tremendously— but you must know what the “clues” mean and how to interpret the data you have collected
- Subtle characteristics of a lesion on MRI scan can greatly help in understanding its cause
  - Mass effect versus enhancement versus restricted diffusion

Case #6: The Teenager Who Began Hitting Her Brother For No Reason
Clinical History

- 18 year old woman who came to ED after witnessed recurrent seizure activity with no history of prior seizures
- Her parents note that a month ago, her personality seemed to change: prone to fits of anger, getting into physical fights with her brother, not paying attention in school or caring about her grades
- Over last week, appeared to be distant, “staring off into space,” not talking more than few words with mumbling speech and possibly having visual hallucinations

Clinical History

- Had first seizure at home and brought to ED where she had several more seizures
- Started on anti-seizure medications and ultimately sedated into medication-induced coma in order to stop seizures completely
- Neurologic examination limited by sedation and patient was too sleepy to participate in examination
- CT Brain and MRI Brain without abnormalities
- CSF showing >50 WBC (normal < 5 WBC)

Encephalitis

- Patient admitted by on-call resident who reviewed her thoughts on morning rounds, highlighting the dramatic personality change and emotional symptoms over the last month followed by more dramatic impairment of language and cognition, and then culminating with status epilepticus
- Given CSF showing evidence of inflammation, the resident felt confident that the patient had either herpes encephalitis or an auto-immune disorder known as NMDA receptor encephalitis

NMDA Encephalitis

- Tends to affect young woman in particular with classic progression from non-specific symptoms of feeling unwell → dramatic personality change and mood changes, hallucinations and paranoia → loss of language function and cognitive disorder → seizures followed by coma and severe instability of heart rate, blood pressure, and body temperature
NMDA Encephalitis

- Auto-immune in nature with antibodies against the NMDA receptors which are part of synapse between neurons in the brain
- 50% of cases are associated with ovarian teratomas: typically benign tumors that contain tissue from many different organ types including brain tissue
- Antibody formation is felt to be immune response to teratoma but then can lead to abnormal cross-reactivity with normal brain tissue
- Treatment is removal of teratoma (if there is one) plus immunosuppression therapy

NMDA Encephalitis History

- First described as a clear clinical entity with association to teratoma only in 2007
- Knowledge and recognition of this syndrome has steadily increased since that time, such that, today, in the right clinical context, a neurology resident in training is able to confidently make a clinical diagnosis of a disorder that no one even knew about 10-15 years ago!
- Now there are accepted diagnostic criteria and treatment algorithms for managing these previously “complete mystery” cases
Googlescholar, PubMed, etc.
- The modern neurologist has the great benefit of having access to the expertise of his colleagues around the world with information readily available due to digitization of medical texts, journals, and case reports
- Helps in diagnosis of rare diseases with distinct features
- Helps in decisions regarding interpretation of diagnostic tests and management
- Supports—but will never replace—the clinical history and neurologic examination which still serves as the foundation for what to search for

Complementary Case to #6
- One of my colleagues was asked to evaluate a young woman in her 20s who had developed sudden deafness as a teenager and now had progressive weakness and difficulty eating
- On examination, she had findings consistent with motor neuron disease (as can be in Lou Gehrig’s disease) but mostly involving the facial and head muscles
- Given her young age, concern was for genetic syndrome
Lessons from Case #6

• Highlights the power of increased medical knowledge and dissemination of information in modern medicine, as a previously unknown clinical entity less than 10 years ago, is now readily recognized by neurologists and other clinicians all over the world
• Importance of on-line "tools" available and how these will continue to improve the practice of diagnosis but also help empower patients and their families with accurate information about their illness

Summary

• Comfort and mastery of "tools" available to neurologists – the focused clinical history, neurologic examination, diagnostic testing, and information from peers around the world – is the first step in becoming an effective diagnostician
• Integrating the tools with knowledge of neuroanatomy helps to quickly localize the area of injury within the nervous system
• For each case, the tools will have weighed importance but are used together to narrow the differential diagnosis
• Diagnosticians must be aware of biases that may lead to errors of judgment or interpretation of clinical data

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References