

TEXAS IMMUNIZATION CONFERENCE 2017

ACUTE FLACCID MYELITIS IN TEXAS

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disclosures

- I have no conflicts or disclosures to disclose in regards to this presentation
- I have clinical research study with Actileon Pharmaceuticals

Infectious Paralysis in Children?

- What can we do if there is a cluster of healthy children who develop profound paralysis with signs of infection?
- Is this a mystery disease?
- Is this the return of poliomyelitis?
- Is this another form of inflammatory, post-infectious central nervous system disease like ADEM or limbic encephalitis?
- We have had answers for this in the past
- We have had new answers for this recently
- We continue to have new questions that need better answers
- I will review this with the perspective from a pediatric provider in Texas
- The CDC has great experience and collected knowledge from across the US, they will share this with us as well

Polio in the US in the 20th century

- Before 1955, paralytic poliomyelitis was a frightening illness that created a reign of terror in the US.
- Crippled thousands of healthy children.
- Epidemics of polio were common up to the early 1950's.
- Public pools were closed, movie theaters were shut, camps and schools were closed.
- National Foundation for Infantile Paralysis via their March of Dimes raised large amount of funds to care for the poor with polio.
- NFIP supported clinical training for polio medical care, and research that led to both the Salk and Sabin vaccines.

Poliomyelitis

- Very common childhood infection, worldwide
- Person-to-person transmission, fecal-oral
- Member of the enterovirus family
- 3 strains of poliovirus
- 100% seropositivity by age 5
- Local and widespread epidemics, pandemic's
- Larger epidemics of polio from late 1800s to 1950s
- Eradication of polio with polio vaccine in the 1950s
- Entry via the GI tract, spread with viremia, tropic to heart, CNS, lung
- Virus can be found in blood, throat, stool

Poliovirus infection

- 95% have asymptomatic infection
- 5% have mild illness
- Less than 1-2% have paralytic polio
- Viremia persists for 3-7 days
- Viremia stops with immune response, antibody to virus
- CNS pathology-viral invasion of anterior horn cells of spinal cord, brainstem, motor cortex with inflammation and necrosis
- Biphasic illness, mild viral illness, improvement for several days, abrupt onset of flaccid paralysis
- Fever, anxiety, muscle pain, focal paralysis, bowel and bladder dysfunction, may have brainstem involvement, bulbar palsy with respiratory distress

Poliomyelitis disease

- Lower extremities more than upper extremity involvement
- Absent reflexes, normal sensation
- Often complete recovery with very mild illness
- Improvement in paralysis over 2 years
- Eradication with polio vaccine
- Inactivated polio vaccine starting in 1955, Dr Jonas Salk
- 16,000 down to 10 cases per year
- Live attenuated polio vaccine starting in 1961, Dr Albert Sabin
- Better protection and herd immunity with live attenuated vaccine in US
- Better protection in the tropics and safer vaccine with inactivated first followed by live attenuated

Transverse Myelitis

- After control of polio with immunization acute paralysis due to polio-like illness is very rare
- Transverse Myelitis, acute paralysis with infection or inflammation in the spinal cord
- Terrifying, like polio pre-1950's
- Fairly rare
- Rapid onset, hours
- Bilateral sensory, motor, and autonomic neurologic disease
- Neurogenic bowel and bladder in 90%
- Paralysis, 70% with LE, 40% with UE
- Sensory changes common, paresthesia, numbness
- Fever, back pain

Transverse Myelitis

- MRI with contrast of spine
- Increased T2 signal involving several spinal cord segments, enhancement
- Sometimes brainstem involvement
- Sometimes cord edema
- Imaging findings can be delayed
- Spinal fluid with pleocytosis, lymphocytes, normal glucose
- No single cause, various causes, demyelinating, auto-immune, post-infectious, infectious w VZV, vasculitis
- Many cases are probably post-infectious-50% have preceding infection, improved for several days, then onset

Transverse Myelitis

- Idiopathic Acute TM, no clear cause, preceding infection is very common
- Some evidence for inflammation as cause, lymphocytes reactive to myelin basic protein, elevated IL-6 in CSF, these decrease w steroids
- Treatment-no organized trials, no randomized clinical trials
- Case reports, small case series
- High-dose steroids first, IV methylprednisolone, 30 mg/kg daily ×5 days, better neurologic outcomes
- If white matter disease then plasmapheresis first
- If not improved then IVIG 1 g/kg daily ×2 days
- Prognosis—slow recovery over months, 80% recovery with steroids, 60% recovery without steroids

Acute Flaccid Myelitis in US, 2014

- Severe viral respiratory infections clustered in children in several places in the US in 2014 with Enterovirus D68, Colorado, California, Illinois
- Cases of acute paralysis with cord disease in children in CO and CA associated with fever and resp illness, some w Enterovirus D68 respiratory infection, late 2014.
- CDC Health Alert in September 26, 2014, Acute Flaccid Myelitis in children
- Search for cases, coordinated diagnostic testing
- Rise and then decline in late 2014
- Pediatric patients, average age 7
- 60% with preceding respiratory illness
- CSF pleocytosis

Acute Flaccid Myelitis 2014

- MRI with gray matter disease in cervical spine
- 1/2 with respiratory infection with enterovirus D68
- Varying degrees of paralysis, 1 limb, 2 limbs, quadriparesis, some cranial nerve involvement
- 20% requiring ventilation
- Paralysis for months or permanently
- 20% with full recovery
- Very few cases in 2015
- Review by expert CDC panel, unclear if this is infectious or post-infectious
- No clear evidence of benefit for polio or enteroviral infection of spinal cord from prior studies with any intervention including steroids and IVIG

AFM experience in Texas 2014

- October 2014, Fort Worth, Texas, Cook Children's Med Ctr
- 4 year old healthy girl
- Sibling with upper respiratory infection
- Fever x3 days, mild cough, mild illness
- Profound weakness in RIGHT upper extremity on the third day
- On exam pronounced weakness RIGHT shoulder, elbow, wrist
- CSF—360 white cells, 90% lymphs, normal glucose and protein

AFM experience in Texas 2014

- MRI of cord with increased T2 signal in central gray cord, edema of cord, no enhancement
- Nasal wash respiratory viral PCR positive Rhinovirus/Enterovirus
- Thorough evaluation otherwise negative
- Treatment for transverse myelitis with IV steroids, IVIG
- Respiratory sample to CDC, positive nasal wash by RT-PCR for Enterovirus D68
- Her weakness persisted afterwards
- She is left with permanent RIGHT upper extremity paralysis

AFM experience in Texas 2016

- 120 cases of AFM in US in 2014
- AFM cases dropped in 2015 nationwide to very low numbers
- AFM cases returned in early 2016, over 100 cases nationwide, several in Texas
- Dell Children's Medical Center in Austin Texas, several cases of AFM in 2016.
- Anxiety among medical providers about possible polio-like outbreak
- Acute transverse myelitis is ordinarily a rare event, few cases
- Early on communication with Austin/Travis County Health Department, Conference call with HD, CDC, DSHS, pediatric infectious disease, pediatric neurology, coordinated efforts to identify cases, define etiology
- Health Advisory alert for AFM by Texas Department of State Health Services, July 6, 2016, 7 cases, 5 in central Texas, 2 in Dallas

AFM experience in Texas 2016

- Dell Children's Medical Center, Austin Texas
- 7 suspected cases
- 6 confirmed cases
- 2 in May 2016
- 2 in June 2016
- 2 in August 2016
- 1 in November 2016
- Poster presentation at Infectious Disease Society of America meeting in October 2017
- Outreach to other providers via Texas Pediatric Society, several centers with cases, San Antonio, Fort Worth, Dallas
- Data collection on other cases in progress with plans for publication

AFM experience in Texas 2016

- 1st case, AD, 7-year-old healthy girl, preceding fever and respiratory illness ×3 days, acute paralysis RIGHT greater than LEFT upper extremity, neck stiffness, 17 white cells in CSF, evaluation low positive Mycoplasma IgM antibody with negative NP Mycoplasma PCR, MRI with gray matter edema of cervical and thoracic cord, nerve root enhancement, treatment with IV and then oral steroids, full recovery, CDC confirmed AFM.

AFM experience in Texas 2016

- 2nd case-CR, healthy 4-year-old boy with fever and mild gastroenteritis for one day then weakness in all 4 extremities, pain and burning in upper extremities, neurogenic bowel and bladder, respiratory distress requiring intubation x 1 week, CSF with 158 white cells, MRI with gray matter edema in cervical spine, brainstem, edema of cord, nerve root enhancement, evaluation negative, treatment with IV steroids, plasma exchange, IVIG, gabapentin, PT, rehab, marked improvement, active ambulatory, but persistent left shoulder paralysis, AFM confirmed by CDC.

AFM experience in Texas 2016

- 3rd case-CC, healthy 5-year-old girl with fever, cough, viral RTI with bronchiolitis x 1 week then rapidly worsening weakness, LEFT upper extremity first then all 4 extremities, neurogenic bowel and bladder, altered mental status, respiratory distress, unresponsive, areflexic on day 3, ventilated, CSF with 120 white cells, MRI with cervical and thoracic gray matter edema, brainstem edema, nerve root enhancement, evaluation positive for **Enterovirus D68** in the rest tract, not in CSF or blood, treated with IV steroids, plasma exchange, IVIG, very slow improvement, tracheostomy, **ventilator** dependent at night, lots of rehabilitation, wheelchair, **quadriplegia**, paralysis LEFT upper extremity, significant weakness in RIGHT upper extremity and both lower extremities, able to do a few normal activities, AFM confirmed by CDC, **AFM with EV D68**

AFM experience in Texas 2016

- 4th case-CR, 4 yr old healthy male with fever and URI 3 days prior to left arm weakness, neck pain and stiffness, left facial, oral weakness, CSF with 145 white cells, MRI with gray matter edema and cervical and thoracic spine, brain stem, nerve root enhancement, evaluation negative, treatment with IV steroids, IVIG, very slow improvement over months but still persistent paralysis in LEFT arm, LEFT shoulder, **not** confirmed by CDC as AFM.

AFM experience in Texas 2016

- 5th case-BG, 6 month old healthy boy with immunizations and URI 2 weeks before mild weakness in both lower extremities and trunk, 16 white cells in CSF, MRI initially normal, repeat with gray matter edema in cervical spine, nerve root enhancement, treated with IVIG, improved, evaluation positive for Parechovirus by culture from stool at reference lab and by PCR from blood, stool and NP at CDC, CSF negative for Parechovirus, AFM with Parechovirus infection, full recovery at 6 months out, confirmed as AFM by CDC.

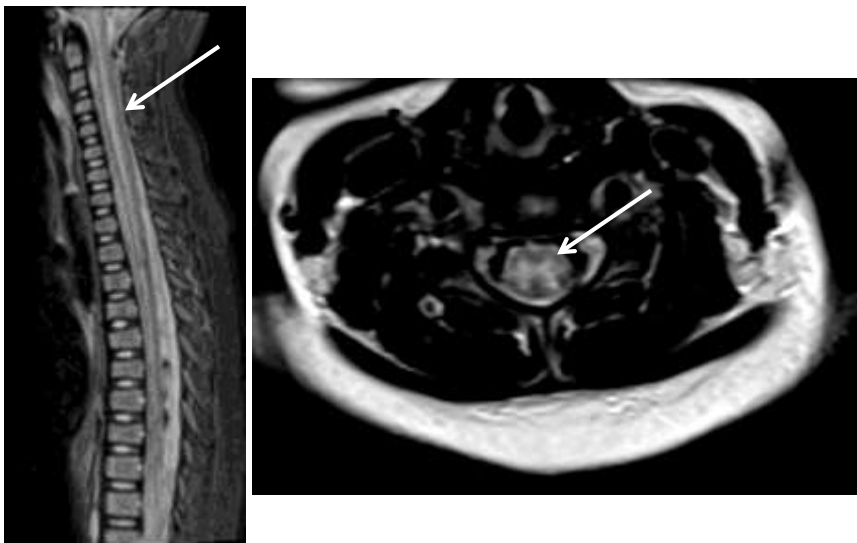
AFM experience in Texas 2016

- 6th case-HR, 13 month old girl with carnitine deficiency, stable, fever for 3 days followed by rash and weakness in both lower extremities and LEFT arm, depressed mental status, seizures, CSF with 43 white cells, CSF positive for **HHV-6** by PCR, 4370 copy/ml, negative repeat CSF and blood, MRI with gray and white matter edema in cervical and thoracic cord, brainstem, basal ganglia edema, , bilateral patchy white matter changes in brain, treatment with IV steroids, IVIG, IV ganciclovir, oral valganciclovir, oral steroids, diagnosis of **ADEM and AFM with Roseola, HHV-6** infection, much improved at 1 month, full recovery at 6 months, probable AFM per CDC.

AFM experience in Texas 2016

- 7th case-MM, 15 month old healthy girl with URI 2-3 weeks before left arm weakness, fever, ataxia, CSF with 150 wbc, MRI with gray matter edema in cervical and thoracic spine, brain stem, nerve root enhancement, cord edema, evaluation positive for **Enterovirus 71**, **Parechovirus** in stool by CDC, treatment with IVIG, fluoxetine, improvement over weeks, full recovery in several months, confirmed as AFM by CDC.

AFM MRI grey matter edema in cord



AFM experience in Texas 2016

- Series of related cases, not all the same illness or etiology
- Ages 6 months to 7 years
- Similar male and female distribution
- Most with preceding viral illness, mostly VRTI
- CSF pleocytosis, 17-158 WBC, mostly lymphs, nl glu, nl prot
- MRI with classis changes of AFM, C and T spine grey matter incr T2 signal, +/- similar brainstem changes, +/- cord swelling, nerve root enhancement
- Treatment like transverse myelitis, IV steroids, IVIG, few w plasma exchange
- Full recovery in most, persistent paralysis in several

AFM experience in Texas

- Some specific diagnoses
- Severe AFM with EV D68 viral respiratory infection with quadriparesis, brainstem involvement, resp compromise, permanent paralysis
- ADEM and AFM with Roseola/HHV-6 infection with full recovery
- AFM with Parechovirus infection with full recovery
- It is unclear if these cases are infectious like polio or post-infectious like idiopathic transverse myelitis
- 2014 cases were more like severe polio with viral infection of gray matter, no response to anti-inflammatory therapy, common permanent paralysis

AFM experience in Texas

- 2016 cases are varied, some likely or clearly post-infectious, many responding to anti-inflammatory therapy, and outcomes much better than 2014, similar to idiopathic transverse myelitis
- One case with probable Enterovirus 71 with mild AFM with full recovery
- Enterovirus 71 is associated with enteroviral syndrome with hand-foot-and-mouth syndrome and occasionally severe encephalitis or polio like paralysis, often in Southeast Asia, not similar to this case
- Encephalitis in children and adults has evolved to more post-infectious etiologies over direct viral infection, ADEM, limbic encephalitis
- Overall much of the experience in 2016 is similar to transverse myelitis, some infectious, many idiopathic/post-infectious/inflammatory

AFM experience in Texas

- With 2014 outbreak CDC has advised that anti-inflammatory therapy may be ineffective and has risks, it should be used with caution
- We need to continue assessing each patient and considering options for therapy
- **Dr Ben Greenberg at UTSW** is a national expert in transverse myelitis, resource for medical care for those affected, has a funded study looking for any patients with TM or AFM who are within 6 months of their event. Any families or clinicians interested can email **Patricia.Plumb@utsouthwestern.edu**
- We will need to continue to gather our best information, use our best judgment, work together to take care of the children in our communities.