NIH Natural History Study of AFM DMID #19-0005

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UAB MEDICINE
PEDIATRICS

Children's of Alabama

AFM Natural History Study
Partnership Across Agencies and Specialties

- CDC
- AFM Work Group
- NIH/NIAID/DMID
- Collaborative Antiviral Study Group

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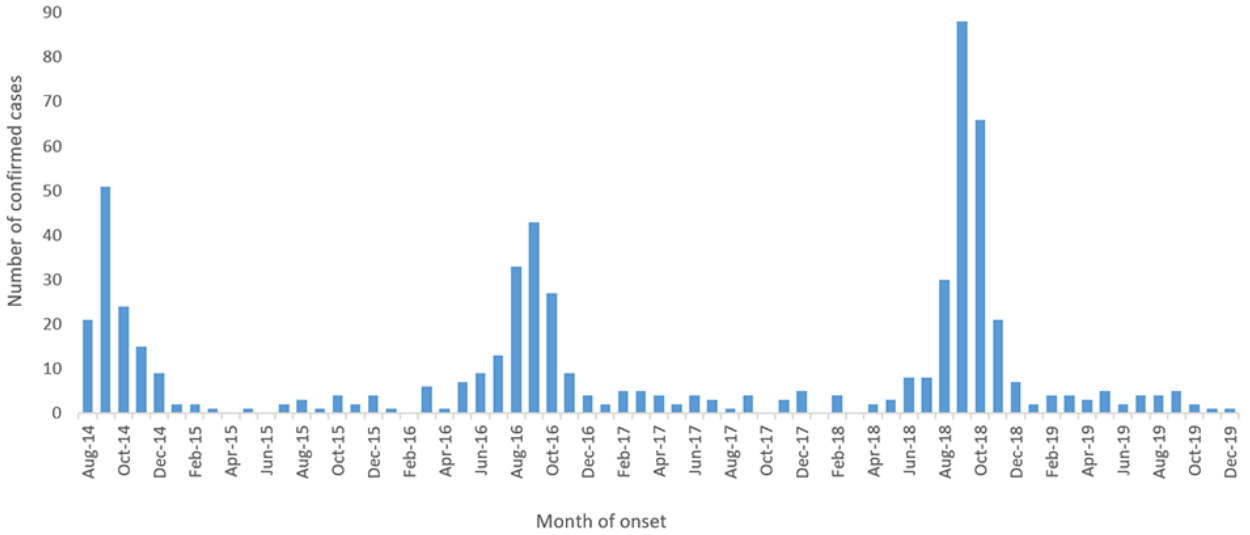

- CDC AFM Task Force
  - Nationwide group of physicians, scientists, and public health experts
  - Variety of disciplines and institutions
  - Review and update clinical guidance on management of AFM patients
  - Better understand the causes of AFM

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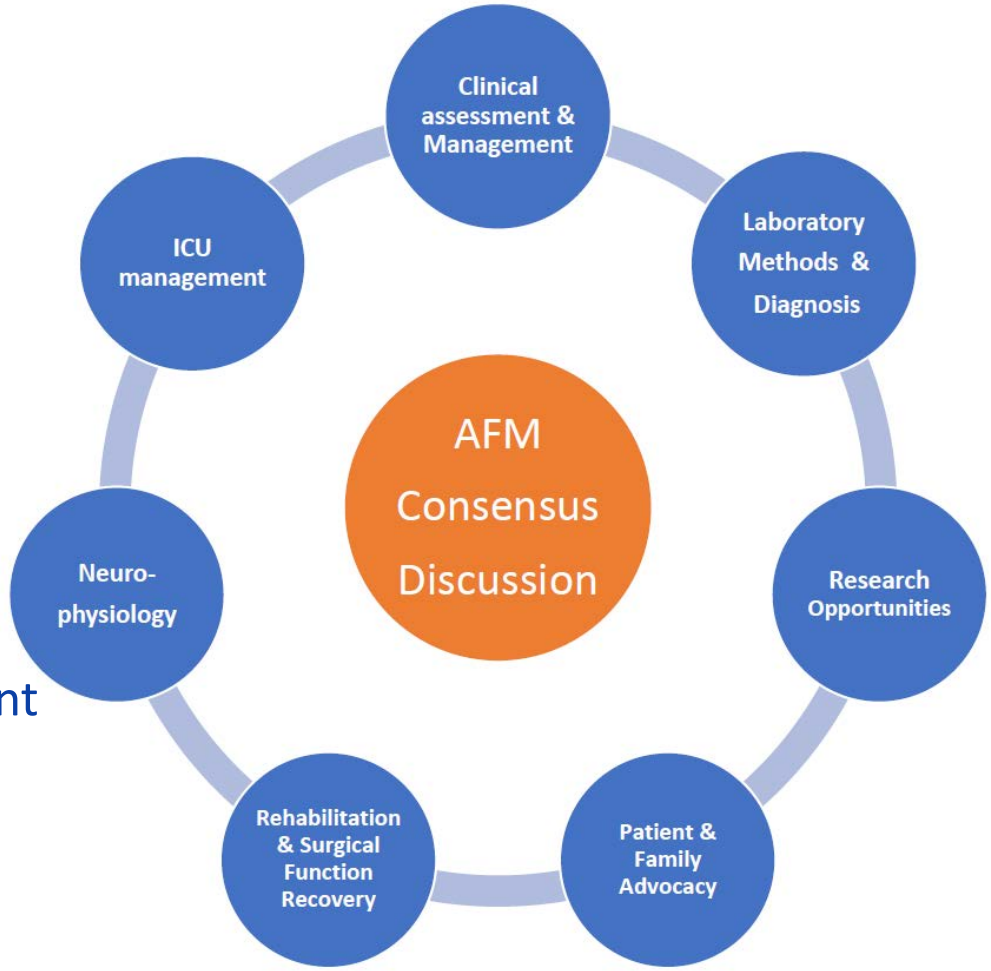

- Objectives:
  - To establish a consensus for diagnosis and management of AFM during the acute and chronic stages of disease
  - Conceive, develop, and conduct collaborative clinical studies to understand the natural history of AFM
  - To facilitate clinical and basic science research to accelerate the discovery of treatment approaches in AFM

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"A major challenge in the study of this disease is that AFM is an uncommon, sporadically occurring complication of a common infection…Research progress is greatly impeded by lack of understanding of the natural history and pathogenesis of AFM disease, including viral pathogenesis, and by lack of understanding of AFM epidemiology…The trajectory of AFM over the past 5 years suggests that the problem is getting worse, and so it is critical that we galvanize our efforts to learn more about, and respond adequately to, this ubiquitous, often crippling, continually reemerging group of viruses."

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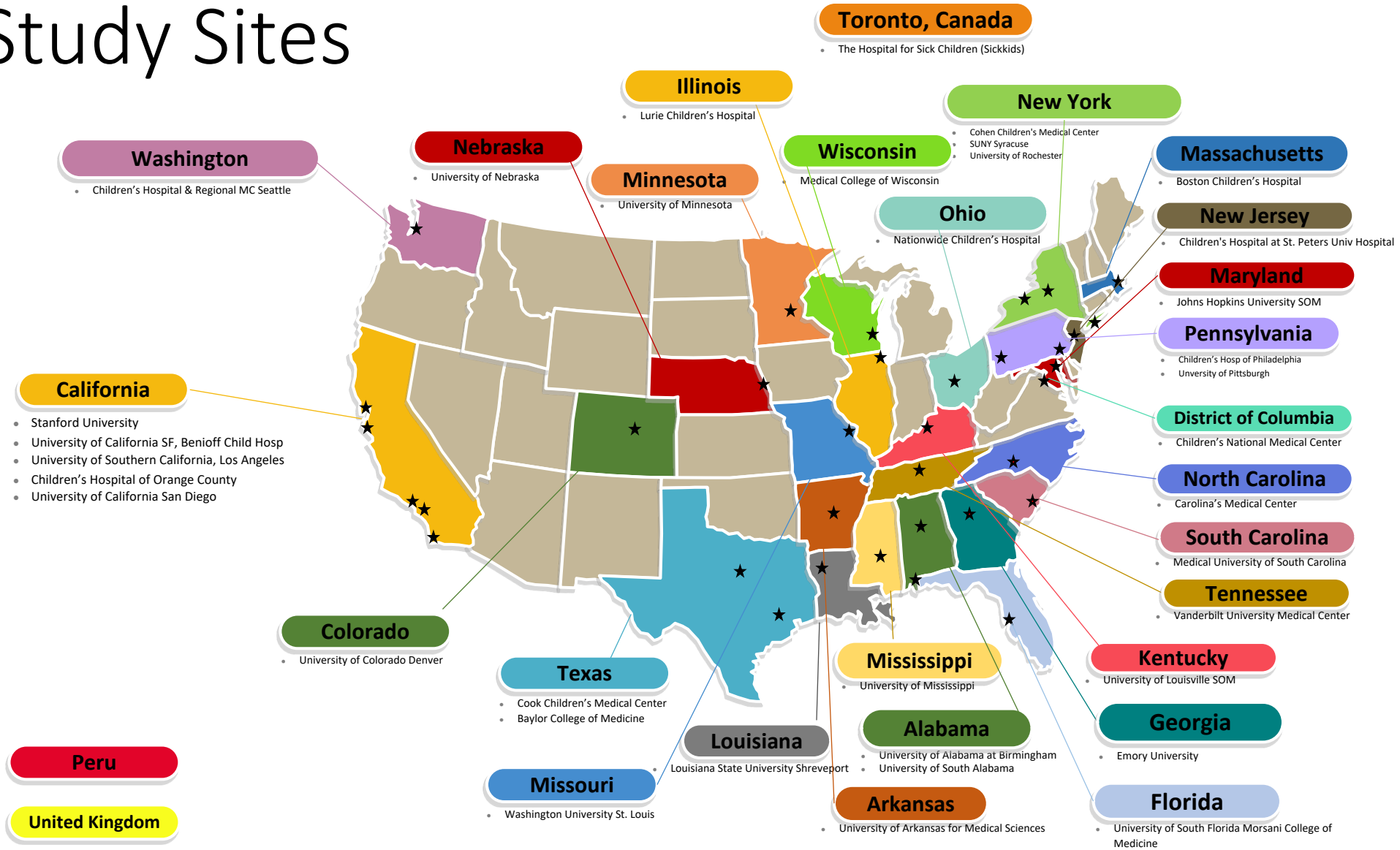
- CDC
- AFM Work Group
- NIH/NIAID/DMID
- **Collaborative Antiviral Study Group**
  - International network of academic institutions, established in early 1970s
  - Natural history and therapeutic studies of rare viral neurologic diseases in children and adults
  - Coordinating Center, Data Management, and Site Management expertise in development and oversight of large multi-center studies

NIAID Acute Flaccid Myelitis Natural History Study Sites



Study Objectives

- Overall:
  - To create a biorepository of specimens and associated clinical and outcome data for use in future studies of AFM, including virologic or immunologic assessments
- Primary:
  - To characterize the epidemiology and natural history of AFM in the first 12 months following enrollment
- Secondary:
  - To describe the diagnostic evaluations and therapeutic interventions that are used in clinical care of suspected AFM cases
  - To identify risk factors for development of AFM
  - To identify determinants of outcome of AFM
  - To describe the clinical characteristics of household contacts of patients being evaluated for AFM

Study Populations

- Inclusion criteria for AFM cases (Group 1, up to 350 subjects) deliberately broader than the CDC case definition
  - Allows inclusion of subjects with less severe manifestations of AFM → can better define clinical spectrum of AFM
- Household contacts of AFM cases (Group 2, up to 350 subjects) also will enroll

Group 1
Inclusion and Exclusion Criteria

Inclusion Criteria:

- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Onset of flaccid limb weakness involving one or more extremities suggestive of possible, probable, or confirmed AFM within previous 30 days
- MRI of spinal cord that has been or will be obtained clinically
- Age < 18 years
- Weight ≥ 7.8 kg
- Agrees to Future Use of Specimens

Exclusion Criteria:

- Known condition other than AFM causing the flaccid limb weakness
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

Note: Subjects enrolling in Group 1 may subsequently be determined by the Protocol Adjudication Committee to not have AFM. This assessment will not occur in real time. If a subject is deemed to have AFM, they will be classified as Group 1A cases (possible, probable, or confirmed AFM cases). If a subject is deemed to not have AFM, they will be classified as Group 1B cases (non-AFM cases) and analyzed accordingly.

Group 2
Inclusion and Exclusion Criteria

Inclusion Criteria:

- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Residing household contact of a child enrolled in Group 1 of this study within previous 30 days
- Weight ≥ 6.0 kg
- Agrees to Future Use of Specimens

Exclusion Criteria:

- Flaccid limb weakness involving one or more extremities
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

Note: If a subject enrolled in Group 2 subsequently develops findings suggestive of AFM, they may be asked if they would like to enroll into Group 1 of the study and be followed and analyzed accordingly.

Group 1 Study Population

- Subjects enrolling in Group 1 (AFM cases) will be assessed by Protocol Adjudication Committee and classified into Group 1A (possible, probable, or confirmed AFM cases) or into Group 1B (non-AFM cases)
  - ~ 70% are anticipated to be classified into Group 1A and 30% into Group 1B
  - This assessment anticipated to occur between the 3 month and 6 month study visits
- Adjudication Committee membership and processes
  - Two standing members who are neurologists and members of the Protocol Committee will review select data for a given subject
  - When in agreement, subject then recorded as Group 1A or Group 1B in database
  - When assessments are discordant, a third neurologist from the Protocol Committee will provide additional review; other Protocol Committee members or of other experts in the field (e.g., neuroradiologists) may be included if needed

	Study Day (window)[a]				Study Month (window)[a]		
	1[b]	3 (± 1 day)	7 (± 2 days)	28 (-18 to +3 days)	3 (± 2 months)	7 (± 2 months)	12 (± 3 months)
Screening and informed consent	X						
Baseline demographics[c]	X						
Detailed patient history	X[d]				X[e]		
Assessment of neurologic illness in household members	X						X
Neurologic examination[f]	X	X	X	X	X	X	X
Neuroimaging by MRI[g]	X[h]						
Nasopharyngeal specimen for biorepository[i]	X	X					
Oropharyngeal specimen for biorepository[i]	X	X					
Serum for biorepository[j]	X		X	X		X	
Whole blood for biorepository[k]	X		X	X		X	
PBMCs and plasma for biorepository[l]	X		X	X		X	
Stool for biorepository[m]	X						
Cerebrospinal fluid for biorepository[g]	X[n]						
Record cerebrospinal fluid indices	X[o]						
Record subsequent hospitalizations[p] and medical diagnoses following study enrollment		X	X	X	X	X	X
Record results of clinical virologic workup				X[q]			
Record results of clinical immunologic workup				X[r]			
Record targeted concomitant medications administered as treatment of AFM	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]
Record therapeutic procedure(s) attempted				X[t]	X[t]	X[t]	X[t]
Record electromyography (EMG) and nerve conduction study (NCS) results[g]	X[u]						
Assessments of degree of neurologic sequelae	X[v]				X[v]	X[v]	X[v]

Studies Not Dictated By Protocol

- Lumbar puncture, MRI, EMG, and NCS evaluations are not required study-related procedures
  - Although MRI of spinal cord that has been or will be obtained clinically is part of Group 1 Inclusion Criteria
- Results and residual specimens will be obtained from studies that are performed for clinical reasons

	Study Day (window)			Unscheduled Sick Visit[b]
	1 (+ 1 day)[a]	7 (± 4 days)	28 (± 9 days)	
Screening and informed consent	X			
Baseline demographics[c]	X			
Detailed patient history[d]	X			
Neurologic examination[e]	X			X[b]
Nasopharyngeal specimen for biorepository[f]	X	X	X	X
Oropharyngeal specimen for biorepository[f]	X	X	X	X
Serum for biorepository[g]	X		X	
Whole blood for biorepository[h]	X		X	
PBMCs and plasma for biorepository[i]	X		X	
Stool for biorepository[j]	X		X	X
Neurologic assessment[k]	X			
Record development of interval illness and final diagnosis			X	

Coordination of Research and Public Health Missions

- Aliquots of samples from the respiratory tract, blood, CSF, and stool of Group 1 subjects will be provided to the CDC for their public health surveillance purposes
- CDC specimens will not be part of the research protocol or biorepository, although virologic and immunologic results of tests performed at CDC may be included in the research database if they are resulted back to the subject's clinical records

AFM Natural History Study Protocol Committee

- Emily Erbelding (NIAID/DMID)
- Walla Dempsey (NIAID/DMID)
- Manisha Patel (CDC)
- Janell Routh (CDC)
- Sarah Kidd (CDC)
- Mark Abzug (University of Colorado Pediatric ID)
- Leslie Benson (Boston Children's Pediatric Neurology)
- Riley Bove (UCSF Neuroimmunology)
- Jessica Carpenter (Children's National Critical Care)
- Charlie Chiu (UCSF Infectious Disease, Virology)
- Roberta DeBiasi (Children's National Pediatric ID)
- Priya Duggal (JHU Genetic Epidemiology)
- Carol Glaser (KP San Francisco Pediatric ID)
- Sarah Hopkins (CHOP Pediatric Neurology)
- Scott James (UAB Pediatric ID)
- David Kimberlin (UAB Pediatric ID)
- Lydia Marcus (UAB Pediatric Neurology)
- Kevin Messacar (University of Colorado Pediatric ID)
- Aaron Milstone (JHU Pediatric Infectious Diseases)
- Kendall Nash (UCSF Pediatric Neurology)
- Carlos Pardo (JHU Neurology, Neuroimmunology)
- Jose Romero (University of Arkansas Pediatric ID)
- Richard Scheuermann (Venter Inst Mol Immunology)
- Greg Storch (Washington University Pediatric ID)
- Elizabeth Wells (Children's National Pediatric Neurology)
- Ann Yeh (University of Toronto Pediatric Neurology)

Second Panel Discussion and Q/A

When to think of AFM
Elizabeth Wells, MD, MHS

Neuroimaging in AFM
Olwen Murphy, MBBCh.

Miss-diagnosis of AFM
Leslie Benson, MD.

AFM Diagnosis and ED
Sarah Hopkins, MD, MPH

NHS of AFM
David Kimberlin, MD.