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A 5 year retrospective study of inflammatory and autoimmune disorders of the nervous system in children at a tertiary academic hospital setting

Study Purpose and Rationale

Diseases that have an inflammatory or autoimmune basis can occur in the brain and spinal cord of young children, and are not restricted to adults. These diseases are rare but can often present in a devastating manner and carry unfavorable long-term prognoses [1]. It is important for physicians training in neurology to be aware of these disorders, as they are the ones who are initially caring for these children. Expanding the education to pediatric emergency medicine physicians and intensivists is crucial to earlier recognition of the heterogeneous symptoms, which may bypass the neurology office and enter the emergency department. In one particular autoimmune disease, N-methyl-D-aspartate receptor (NMDA-R) encephalitis, retrospective reviews have demonstrated that earlier onset of treatment in both children and adults, result in better clinical outcomes [2,3]. NMDA-R encephalitis is particularly important to diagnosis and treat early, with up to a 25% mortality rate and up to 18 month recovery in survivors (i.e. poor quality of life) [4].

Many of these diseases have been described as a single disorder. To date, there is not a description of these diseases all together in a single paper. The purpose of this study is to look at all of the children who have presented to the NY Presbyterian Morgan Stanley Children's Hospital within the last five years with the following diseases: acute demyelinating encephalomyelitis (ADEM), acute transverse myelitis (TM), multiple sclerosis (MS), neuromyelitis optica (NMO), NMDA-R encephalitis, neuropsychiatric syndromes associated with lupus (CNS lupus), primary central nervous system (CNS) vasculitis, and the opsoclonus myoclonus ataxia syndrome (OMS). We would like to examine patterns of initial presentation, patterns in the blood and other diagnostic tests, and outcomes for these children. Our hope is that we will be able to teach future physicians about these rare disorders so that they know how to recognize them and manage them promptly. In doing so, we believe that we can improve the lives of the children that are affected by these inflammatory disorders.

We hypothesize that there will be a change towards more prompt identification and aggressive treatment of these diseases in later years of analysis. Further, we hypothesize that specific biomarker patterns will emerge for these diseases.

Study Design and Statistical Procedures

In this study, we will be analyzing data from all of the subjects diagnosed with a neuro-immunologic disorder at this institution from 2010 to 2015. We will collect data specifically on the following diseases: acute demyelinating encephalomyelitis (ADEM), acute transverse myelitis (TM), multiple sclerosis (MS), neuromyelitis optica (NMO), N- methyl D-aspartate receptor (NMDA-R) encephalitis, neuropsychiatric syndromes associated with lupus (CNS lupus), primary central nervous system (CNS) vasculitis, and the opsoclonus myoclonus ataxia syndrome (OMS). Information to be collected will include clinical information from charts including initial presentation, workup (both inpatient and outpatient), initial and

maintenance treatment regimens, level of acuity, duration of hospitalization, and clinical outcome at last follow up. We will also collect information on rehabilitation outcomes.

Since this is a retrospective case study, we will be comparing individual subjects and making subgroup analyses based upon the data retrieved. Subgroup analysis initially will be based on disease subtype and age at presentation. The primary outcomes are the length of hospital stay and neurologic outcome at follow-up. Secondary outcomes include CSF protein, CSF glucose, CSF white count, CSF oligoclonal bands, CSF IgG index, MRI T2/FLAIR patterns, EEG patterns, percentage of subjects with seizures (clinically or on EEG), and percentage of subjects requiring rehab. Summary statistics will be calculated for relevant variables.

Chi-squared test can be used to assess the categorical variables in the study. If we anticipate that 50% of subjects recover in the less aggressively treated group versus 60% in the more aggressively treated group by 4 week follow-up, we can estimate needing 90 subjects in each group for a power of 0.8 and $p<0.05$. Given the rarity of these diseases in the general population, we will need to recruit patients from other hospitals to reach these numbers.

Study Procedures

This will be a retrospective chart review from January 2010 to December 2015. Medical records from all admissions to New York Presbyterian Morgan Stanley Children's Hospital or visits at the pediatric neurology practice at Columbia Doctors in Harkness Pavilion 5th floor or 3rd Floor Vanderbilt Subspecialties clinic affiliated with New York Presbyterian for children 18 years or younger during this time period with the following International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes will be collected:

Demyelinating disease
Multiple sclerosis – 340
Neuromyelitis optica – 341.0
Demyelinating disease of central nervous system unspecified – 341.9 Other demyelinating diseases of central nervous system – 341.8 Infectious acute disseminated encephalomyelitis – 323.61

Encephalitis:
Encephalitis and encephalomyelitis following immunization procedures – 323.51 Other postinfectious encephalitis and encephalomyelitis – 323.62
Other causes of encephalitis and encephalomyelitis – 323.81
Unspecified causes of encephalitis, myelitis, and encephalomyelitis - 323.9 Encephalitis, myelitis, and encephalomyelitis 323

Vasculitis:
Cerebral arteritis – 437.4

Myelitis:
Postinfectious myelitis – 323.63

Other causes of myelitis – 323.82
Acute (transverse) myelitis – 341.20
Acute (transverse) myelitis in conditions classified elsewhere – 341.21 Idiopathic transverse myelitis – 341.22

OMS:
Other irregularities of eye movements – 379.59

Cerebellar ataxia:
Other cerebellar ataxia – 334.3
Cerebellar ataxia in diseases classified elsewhere - 334.4

Study Subjects
The study population is children 18 years or younger treated at New York Presbyterian Morgan Stanley Children's Hospital diagnosed with inflammatory and autoimmune disorders affecting the nervous system.

Participant Inclusion Criteria: All children presenting to the New York Presbyterian Morgan Stanley Children's Hospital and its affiliate pediatric neurology clinics at age 18 years or younger with the ICD-9 codes listed above will be included in this study.

Participant Exclusion Criteria: As these diseases are quite rare in the pediatric population, no specific segment of the population will be excluded.

Informed Consent Process
No consent will be obtained from the subjects or parents for this chart review.

Confidentiality of Study Data
The study team will acquire a list of records as described above for review. Protected Health Information (PHI) will only be collected to ensure no duplication of charts reviewed. All PHI will be coded per CUMC policy after data collection.

Data will be available only to study team members on a data collection form. The form will contain no specific patient identifiers. The information on this form will be transferred to an excel spreadsheet and stored on a password protected jump drive. The jump drive will be accessible to team members only. No patient identifiers will be recorded in the excel spreadsheet. Recorded information will include information collected in Appendix A.

Recorded information will include: initial presentation, acute treatment in the hospital, duration of hospitalization, level of acuity (ICU stay and length), biomarkers (EEG, CSF, and imaging), consultations obtained during the care, length of stay in rehabilitation, outpatient treatment and clinical outcome at last follow up. The information will be collected by study team members and will be recorded into a password encrypted excel file on the

Babylon file server (certified as per the published CUMC IT Certified Environment List, System ID:566) and coded so that the data may be linked to the participants. Any paper documents will be coded and stored in a locked file cabinet that the principal investigator and research coordinator will have access to. Only the principal investigator and the research coordinator will have access to the identifiable data/code key which will also be kept in a password protected file on the secure Babylon file server.

Potential Risks
No potential risks foreseen as this is a retrospective medical chart review.

Potential Benefits
There are no direct benefits to the subjects in this study, as it is informational only and may only have indirect benefits in the future care of other subjects with neuro-immunologic diseases.

Appendix A
Data Collection Form

Subject Name: Subject MRN:
Age at Presentation (years):

1) initial presentation
2) other medical history/comorbid conditions
3) acute treatment in the hospital
4) duration of hospitalization
5) level of acuity (ICU stay and length)
6) biomarkers (EEG, CSF, serum autoantibodies and inflammatory markers, and imaging)
7) consultations
8) length of stay in rehab
9) outpatient treatment
10) clinical outcome at last follow-up

References

1. Pohl D. Epidemiology, immunopathogenesis and management of pediatric central nervous system inflammatory demyelinating conditions. Curr Opinion Neurol 2008;21(3):366-372.
2. Byrne S, Walsh C, Hacohen Y, et al. Earlier Treatment of NMDAR Antibody Encephalitis in Children Results in a Better Outcome. Neurol Neuroimmunol Neuroinflamm 2015;2:e130.
3. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157-165.
4. Barry H, Byrne S, Barrett E, et al. Anti-N-methyl-D-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. BJPsych Bull 2015;39(1):19-23.