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Early Functional Outcomes for Pediatric Patients Diagnosed with Anti-NMDA Receptor Encephalitis during Inpatient Rehabilitation

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Abstract

Objective: The aims of the current study were to characterize the demographic and clinical presentation of pediatric patients diagnosed with anti-NMDA receptor encephalitis who require inpatient rehabilitation, to examine early functional outcomes, and to investigate predictors of early recovery.

Design: A retrospective chart review was conducted for 27 pediatric patients diagnosed with anti-NMDA receptor encephalitis who received intensive inpatient neurorehabilitation.

Results: On average, patients were 10.6 years of age (range 2-18) at the time of symptom onset. Average time to treatment from symptom onset was 27.2 days (range 5-91). Patients displayed significant improvements between admission and discharge WeeFIM DFQ scores across patients ($p<.01$). Mean WeeFIM Total DFQ score at admission was 28.6 (range 15.0 – 62.6) and at discharge was 54.3 (range 14.2 - 91.9). Younger age at onset, seizures, and number of treatments received was associated with worse functional outcomes at discharge. Time to initiate treatment was not found to be associated with early functional outcomes.

Conclusion: Pediatric patients diagnosed with anti-NMDA receptor encephalitis displayed significant functional gains during inpatient rehabilitation, despite persistent functional deficits at discharge, suggesting the need for ongoing monitoring and intervention.

Key words: autoimmune; encephalitis; pediatrics; rehabilitation

Introduction

Anti-NMDA receptor encephalitis is a recently described autoimmune disorder with a predictable clinical course.[1] An autoimmune reaction is thought to be triggered that results in the production of antibodies targeting against the glutamate NMDA receptor, specifically the R1 subunit.[2] The NMDA receptor is a glutamate receptor, which is a major excitatory neurotransmitter in the central nervous system (CNS). As the brain ages, the NMDA receptor system becomes progressively hypofunctional, contributing to memory and learning impairments. Dysfunction of the NMDA receptor has also been implicated in other conditions such as schizophrenia, epilepsy, and dementia.[2]

Anti-NMDA receptor encephalitis was first described in 2007 by Dalmau and colleagues. It is characterized as a paraneoplastic syndrome that was observed in young women of child bearing age who were found to have ovarian teratomas and presented with new onset psychosis or memory problems that progressed to include multiple neurological deficits.[3] Patients often required prolonged hospitalization and recovery time; nevertheless, they typically responded positively to immunotherapy treatment. While the incidence is unknown, epidemiological studies suggest that anti-NMDA receptor encephalitis may be the second most common autoimmune cause of encephalitis following acute disseminating encephalomyelitis (ADEM).[2,4,5] Given the high frequency of psychiatric symptoms at presentation, patients may be improperly diagnosed and/or admitted to a psychiatric hospital, which impacts time to diagnosis and treatment.

A large observational study examined the demographic and clinical characteristics of 577 patients diagnosed with anti-NMDA receptor encephalitis.[6] Findings revealed that a majority of patients were female (81%) and 1/3 of patients were younger than 18 years of age. The presence of a tumor was most common in females between the ages of 12-45 years of age, with 94% of

identified tumors being an ovarian teratoma. African American and Asian patients were more likely to have a tumor compared to Caucasian or Hispanic patients. Regarding initial symptoms, approximately 50% of children younger than 12 years of age presented with seizures or movement disorders whereas 65% of adults presented with behavior and/or personality changes. Adolescents tended to present with a combination of symptoms. Regardless of age, the most common cumulative symptoms included behavior changes and cognitive deficits, memory deficits, speech disorder, seizures, movement disorder, and decreased level of consciousness. One recent study found possible gender differences for presenting symptoms, with female patients being more likely to initially present with psychiatric symptoms compared to male patients who more frequently experienced seizures at symptom onset.[7]

Despite the increasing interest in Anti-NMDA receptor encephalitis, few studies have addressed the acute and long term functional outcomes of these patients, particularly within pediatrics. In the original case series with adults, approximately 75% of patients were found to have a "full recovery" or mild persistent deficits, which was determined by return to work or return to most activities of daily living.[1] Authors indicated better outcomes and fewer relapses for patients who were found to have a tumor and received early treatment, including tumor resection and immunotherapy. The mechanism that initiates this disorder is unknown, especially when there is no tumor present, which is thought to trigger an immune response. Despite substantial recovery, relatively few studies have reported on the functional or cognitive outcomes of patients with anti-NMDA receptor encephalitis, particularly in children.

In a recent case series of 6 pediatric patients diagnosed with anti-NMDA receptor encephalitis, Houtrow and colleagues (2012) reported good progress during inpatient rehabilitation, despite persistent functional deficits at discharge based on WeeFIM scores.[8] Finke

and colleagues (2012) examined cognitive deficits in a sample of 9 adults who were, on average, 28 years of age (range=21-44) and approximately 43 months out from symptom onset (range=23-69 months).[9] Persistent cognitive deficits were found in a majority of patients (8 out of 9), particularly in the areas of executive functioning and memory. Researchers also found that patients who received earlier treatment (e.g., within three months of symptom onset) performed significantly better on cognitive domains, suggesting the potential benefit of early diagnosis and treatment for these patients. In a case study of a 29-year-old female, Vahter and colleagues (2014) found persistent memory deficits at long-term follow-up (608 days from onset).[10]Across studies, the neurocognitive domains often impacted include processing speed, executive functioning, memory, and language fluency, with more notable deficits being reported within the acute recovery period and among patients who had delayed immunotherapy.[1,11–13]

The patterns and predictors of recovery from encephalitis in general, and anti-NMDA receptor encephalitis more specifically, are poorly understood as there is limited research in pediatrics. In a case series examining the functional status of children with various forms of encephalitis in an inpatient rehabilitation setting, Tailor and colleagues (2013) concluded that patients demonstrated significant functional gains as demonstrated by change in WeeFIM scores; nevertheless, the degree of recovery was variable across patients.[14] While previous studies have noted a generally favorable cognitive recovery in adults, little is known about the early functional outcomes in pediatric patients diagnosed with Anti-NMDA receptor encephalitis who require inpatient rehabilitation.[14]

The aims of the current study are: (1) to characterize the demographic and clinical presentation of pediatric patients diagnosed with anti-NMDA receptor encephalitis who require inpatient rehabilitation; (2) to examine the early functional outcomes of these patients in an

inpatient rehabilitation setting; and (3) to investigate predictors of early recovery, including age, the presence of disease complications, time to treatment, and number of treatments received. We hypothesize that patients will display notable gains in functional status during inpatient rehabilitation, although they will display persistent functional deficits at discharge. Based on the existing literature, we hypothesize that younger age, the presence of disease complications, longer time to initiate treatment, and number of treatments received will be associated with worse functional outcomes and greater impairments in functional skills at the time of discharge from inpatient rehabilitation.

Methods

Participants

A total of 27 patients were identified with a diagnosis of anti-NMDA receptor encephalitis who were admitted to the inpatient rehabilitation unit following acute care hospitalization. During the inpatient admission, patients participated in daily speech/language therapy (SLT), occupational therapy (OT), and physical therapy (PT) services for a total of three hours. Functional status was evaluated upon admission and discharge by the child's primary rehabilitation therapists using the Functional Independence Measure for Children (WeeFIM). Neuropsychology also assisted with serially monitoring of cognitive status. Patients received ongoing medical and medication management by the medical team.

Procedures

Data was gathered through retrospective chart review of patients seen between 2010 and 2017 who were diagnosed with anti-NMDA receptor encephalitis and admitted to the inpatient rehabilitation unit (N=27). Institutional Review Board (IRB) approval was obtained. Due to the retrospective nature of this study and the fact that assessments are conducted as a part of routine

clinical practice, the study met criteria for Waiver of Consent. Demographic and clinical variables of interest were gathered through retrospective chart review, including gender, ethnicity, age at onset, initial and cumulative symptoms, results of the diagnostic work-up, treatments and medications received as well as functional status upon admission to and discharge from the inpatient rehabilitation setting.

Measures

Functional Independence Measure for Children – Second Edition (WeeFIM). The WeeFIM is an 18-item, performance-based measure that assesses mobility, self-care, and cognition in the rehabilitation setting.[15] Given the wide range of scores and the effect of age on these ratings, WeeFIM Developmental Functional Quotients (DFQ) were calculated and used.[14] DFQs are calculated by dividing the child's raw score by the age-based normative scores and multiplying that number by 100 to reflect the percent of "normal" or "age-appropriate" functioning, thus allowing for comparison of scores across age groups. An age appropriate DFQ score is 100.

Treatment Variables. Time to treatment was defined as the number of days from symptom onset to the initiation of first or second line treatment (e.g., steroids, intravenous immunoglobulin [IVIG], plasma exchange [PLEX], rituximab, cyclophosphamide). Number of treatments received reflects the number of first and second line treatments received during the disease course, ranging from 1 to 5. The length of stay (LOS) on the inpatient rehabilitation unit was defined as the number of total days a patient was on the unit.

Data Analyses

All statistical analyses were completed using SPSS 20.0[16] with alpha set at $p < .05$. Descriptive analyses of demographic and clinical variables were conducted to characterize the

participant group. Paired sample t-tests were used to examine differences in WeeFIM DFQ scores between admission and discharge ("recovery of functional skills"). Bivariate correlation analyses were conducted to examine the relationship between age at onset, time to treatment, LOS, and discharge WeeFIM DFQ scores. Finally, exploratory analyses, including independent sample t-tests, chi square tests, and analyses of covariance (ANCOVA) were used to examine predictors of early functional outcomes (e.g., age, presence of disease complications, time to treatment, number of treatments received).

Results

Demographic and Clinical Characteristics

Demographic and clinical variables of interest are presented in Tables 1, 2, & 3. Descriptive analyses revealed that patients were, on average, 10.6 years of age (SD=5.2; range=1.98-18.3) at the time of symptom onset. A majority of patients were female (63%). The sample was diverse, with 63% of patients being African American compared to a smaller percentage of Caucasian or Hispanic patients. The most common initial symptoms included flu-like symptoms, behavioral changes, or altered mental status. In addition, the most common cumulative symptoms included insomnia, mutism, and agitation. The average time to initiate first or second line treatment from symptom onset was 27.2 days (range = 5 – 91; SD = 18.9). LOS on the inpatient rehabilitation unit ranged from 14 to 108 days (M = 39.0, SD = 20.1).

Neuroimaging (MRI) and EEG findings were abnormal at some point in the disease course for 52% and 70% of patients, respectively. As expected, a majority of patients had abnormal cerebrospinal fluid (CSF) or serum findings to confirm the diagnosis of anti-NMDA receptor encephalitis. Consistent with the pediatric literature, only a small percentage of patients in our sample were found to have a teratoma (n=4; 12%). With regard to treatments, a majority

of patients received steroids and/or IVIG as first line treatments. Approximately half of the patients received PLEX and 70% received rituximab. The use of cyclophosphamide was less common amongst our patients. A majority of patients received at least three first or second line treatments (~75%). A variety of medications were also used for symptom management.

Recovery of Functional Skills

The WeeFIM DFQ scores were examined at admission and discharge using paired sample t-tests. Significant improvements were seen between admission and discharge total (t = -5.63, p <.01) and domain scores (cognition t = -5.06; self-care t = -5.53; p <.01; mobility t = -5.27, p <.01), see Figure 1. The majority of children made gains in functional status with an average change in WeeFIM Total DFQ scores of 25.3 percentage points (range: -7.9 - 75.2, p < .01). Mean WeeFIM Total DFQ score at admission was 28.6 (range: 15.0 – 62.6) and at discharge was 54.3 (range: 14.2 - 91.9).

WeeFIM discharge DFQ scores were further examined to determine the level of dependence at discharge. A cut-off score of < 30 was used to represent dependent functioning, scores between 30-84 were used to represent partial dependence, and scores > 85 were used to represent independent or "age appropriate" functioning.[14] Approximately 8% of patients had discharge WeeFIM Total DFQ scores suggestive of independent or "age appropriate" functioning, 35% were below age expectations or "partially dependent," and 56% were well below age expectations or "dependent." Hence, despite functional improvements seen for most patients throughout admission, a majority of patients continue to display persistent functional impairments at discharge from inpatient rehabilitation (Figure 2).

Predictors of Early Functional Outcomes

WeeFIM Total DFQ admission scores were significantly correlated with WeeFIM Total DFQ discharge scores (r = .52, p <.01). Age at onset was correlated with WeeFIM DFQ total (r = .53, p <.01) and domain scores at discharge (Cognition: r = .44, p <.05; Self-care: r = .54, p <.01; Mobility: r = .51, p <.01). LOS was also significantly correlated with WeeFIM DFQ total (r = -.41, p <.05), cognition (r = -.44, p <.01), and self-care (r = -.39, p <.05) scores at discharge, such that longer LOS in rehabilitation was related to worse functional outcomes. Time to treatment was not found to be correlated with WeeFIM DFQ scores at admission or discharge.

Independent sample t-tests were conducted to examine relationships between demographic and disease characteristics with early functional outcomes. Similar to the TBI literature, we expected that younger children may be more vulnerable to worse outcomes given vulnerabilities associated with brain disruption earlier in development. With regard to age, results revealed that patients younger than 8 years of age had lower discharge WeeFIM DFQ total (t = -3.28, p <.01), cognition (t = -2.69, p <.05), self-care (t = -3.54, p <.01), and mobility scores (t = -2.79, p <.05) compared to children older than 8 years of age. Patients older than 8 years of age were also more likely to present with or display psychosis (χ^2 = 7.56, p < *.01*). No significant relationship was found between positive neuroimaging findings and functional outcomes.

With regard to disease complications, an ANCOVA was conducted to determine the impact of seizures on functioning above and beyond the effects of age. Results indicated that patients who experienced seizures at any point in their disease course were more likely to have a flat change profile on WeeFIM scores from admission to discharge (F [1,23] = 16.94, p <.01), as well as lower functioning on WeeFIM DFQ total (F[1,23] = 5.82, p =.024), mobility (F[1,23] =

5.86, p = .024) and cognition scores (F[1,23] = 7.39, p = .012), above and beyond the effects of age, compared to patients who did not experience seizures. There was no significant difference between the seizure and non-seizure group on WeeFIM DFQ self-care domain scores.

The influence of time to treatment was also examined. No significant relationship was found between time to treatment (i.e., symptom onset to first or second line treatment) and early functional outcomes (WeeFIM DFQ admission scores), which may be further impacted by a lack of statistical power and/or reflective of the small sample size. Finally, the number of first or second line treatments received was examined. There was a significant correlation between number of treatments received (ranging from 1 to 5) and admission WeeFIM DFQ scores (total r = -.46, p <.05; cognition r = -.42, p <.05; self-care r = -.40, p <.05; mobility r = -.44, p <.05), such that patients who presented with lower admission WeeFIM DFQ scores received a higher number of first and second line treatments. In addition, there was a correlation between number of treatments received and total WeeFIM DFQ discharge scores (total r = -.43, p <.05).

Discussion

The current study sought to characterize the demographic and clinical presentation of pediatric patients diagnosed with anti-NMDA receptor encephalitis who require inpatient rehabilitation. This study also examined early functional outcomes of these patients and investigated predictors of early functional recovery. Similar to previous studies, our sample was predominantly female, with only a small percentage of our pediatric patients having a teratoma. A majority of our sample was also non-Caucasian. While the racial and/or ethnic background of patients diagnosed with anti-NMDA receptor encephalitis is not consistently reported, more research is needed to investigate the potential role that ethnic and/or racial background may have on disease occurrence.

Consistent with our hypotheses, patients displayed significant gains in functional status across admission, although they continued to display persistent functional deficits at discharge. Results also confirmed that younger children and the presence of disease complications, namely seizures, were associated with worse functional outcomes and greater impairments in functional skills at discharge from inpatient rehabilitation. Additionally, longer LOS in rehabilitation was similarly related to worse functional outcomes, likely suggesting that those patients with a longer LOS may have been more medically complicated. Time to initiate treatment was not found to be associated with early functional outcomes.

Similar to recent studies, a majority of our patients demonstrated significant improvements on WeeFIM DFQ scores across total and domain scores during inpatient rehabilitation.[6, 10] Improvements in functional skills suggest the benefit of intensive inpatient neurorehabilitation early in the recovery course for pediatric patients with anti-NMDA receptor encephalitis. However, despite overall improvements, only a small proportion of patients were deemed "independent" at the time of discharge with approximately 25-40% of our sample remaining "dependent" across functional abilities, most notably within the cognitive domain.

A small cohort of patients exhibited a limited or flat change profile in WeeFIM scores between admission and discharge. Previous studies have also noted a similar subset of patients who tend to fair worse, either declining or showing minimal gains, across an inpatient rehabilitation admission[14]. Specifically, in our sample, two patients exhibited a decline in WeeFIM total raw score, while eight patients exhibited limited to no change in total, self-care, or mobility scores from admission to discharge. Of note, twelve patients exhibited limited to no change in the cognitive domain scores. Clinically, we notice that patients who exhibit little or no improvement at discharge in the rehabilitation setting tend to be more neurologically complex,

such as having seizures, and require more medications. Additionally, it may be that these patients are younger in age. This intriguing finding lends to an opportunity for future studies to examine this group of "poor responders."

In line with previous studies on pediatric brain injury, age at the time of illness was also associated with worse functional outcome at discharge.[17,18] In our sample, younger children tended to fair worse, with less improvements and more dependence on others at the time of discharge. Although there is some evidence within the existing anti-NMDA receptor encephalitis literature to support the important role of age, there is a paucity of research exploring the relationship between age and functional outcome. Some studies have suggested that younger children tend to be more neurologically complex, which may be the driving predictor of outcomes. Further studies addressing the impact of age within this population is clearly needed.

There also continues to be a notable paradox in anti-NMDA receptor encephalitis, with patients presenting with significant neurological deficits and decline, yet normal neuroimaging findings, particularly at symptom onset. Approximately 35-50% of cases may have abnormal neuroimaging findings, although abnormalities are often non-specific.[3,6,19,20] While limited, some recent studies have demonstrated resolution of abnormalities following immunotherapy treatment, including diffuse cerebral atrophy.[21,22] Newer research has also suggested that this disease may be associated with alterations of functional connectivity and widespread changes of white matter integrity, despite normal findings in routine clinical MRI.[23] While there was not a significant relationship found between positive neuroimaging findings and functional outcomes in our sample, there was a trend toward significance for positive MRI findings at some point in the disease course with WeeFIM DFQ cognition score at discharge, suggesting that a larger sample may produce a significant relationship.

Contrary to our hypotheses, we found that time to first or second line treatment was not predictive of acute functional outcomes, such that those patients who received these treatments the quickest were not necessarily the ones showing the most improvement in their early recovery. Previous studies have suggested that first and second line treatments are important for both quicker and more improved recovery of function.[9] However, specific randomized control trials have not been done and thus, it is difficult to come to this conclusion. Additionally, presentation of symptoms with this disease is quite variable, which often makes it difficult to determine exactly when symptom onset occurred. Further, patients are often prescribed additional medications prior to admission to inpatient rehabilitation for symptom management (e.g., antipsychotics, anti-epileptics), which could complicate their recovery trajectory and potentially interfere with the effectiveness of first and second line treatments. It will be important for future research to consider ways of determining symptom onset as well as evaluating treatment effectiveness.

The current findings need to be considered in the context of several limitations. First, the sample size for this cohort is relatively small and some relationships between variables may not have been significant due to reduced power. Additionally, the anti-NMDA receptor encephalitis patient group is quite heterogeneous and there is a great deal of variability with regard to course, treatments received, timing of treatments, as well as role of other medications. Findings are also based on retrospective medical chart review. Many patients presented to outside hospitals at onset or during acute hospitalization; hence, there are varying details available regarding the acute hospital course prior to the transfer to inpatient rehabilitation. Finally, the current cohort potentially represents a biased sample, given that they all required inpatient rehabilitation. Early functional outcomes may look different for those pediatric patients diagnosed with anti-NMDA receptor encephalitis who did not require this intensity of rehabilitation (e.g., inpatient

rehabilitation). Current findings report on the early functional outcomes using WeeFIM scores, a measure commonly used in the inpatient rehabilitation setting, which may limit the generalizability of findings to functioning in the everyday environment. Further, the WeeFIM has not been validated as an outcome measure specifically for patients with anti-NMDA receptor encephalitis. Therefore, additional research is needed to better characterize the long-term functional and cognitive outcomes of these patients using standardized psychological assessment measures, particularly following the acute recovery phase.

Conclusions

Children and adolescents diagnosed with anti-NMDA who require inpatient rehabilitation display significant functional improvements during inpatient rehabilitation; however, they continue to display persistent functional deficits at discharge. Response to treatment and degree of improvements are variable across patients, with a majority of patients remaining at least partially dependent at discharge. The current sample revealed a group of "poor responders," which warrants further investigation. This study suggests that younger age, the presence of seizures, and greater number of treatments received was associated with worse functional outcomes at discharge. Other demographic and clinical variables were not associated with early functional outcome. Hence, it will be important to conduct comprehensive neuropsychological assessments to better characterize cognitive deficits and recovery trajectory. Future studies should continue to explore predictors of long-term functional recovery (e.g., age, presence of disease complications, time to treatment, medications, impact of premorbid risk factors). Further, it will be necessary to examine demographic and clinical variables for those patients who did not require intensive rehabilitation to identify any differences that may predict a more or less severe course. Current findings highlight the need for ongoing monitoring of these patients over time to better characterize outcomes and to investigate the longitudinal trajectory of recovery over time.

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Table 1

Demographic and Clinical Variables

Table 2

Diagnostic Test Results

Table 3

Treatments Received

Figure 1

Box Plots of Admission and Discharge WeeFIM DFQ Scores

Note: This figure shows box plots of admission and discharge WeeFIM DFQ scores for each domain and total score. For each box plot, the median score is indicated by a bold line, the interquartile range by the top and bottom of the box, and the non-outlier range by the "whiskers" extending beyond the box.

Figure 2

Level of Dependence at Discharge from Inpatient Rehabilitation

Figure 1

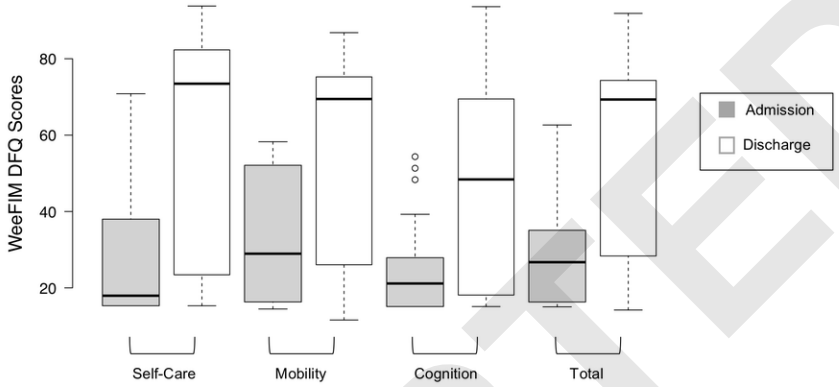
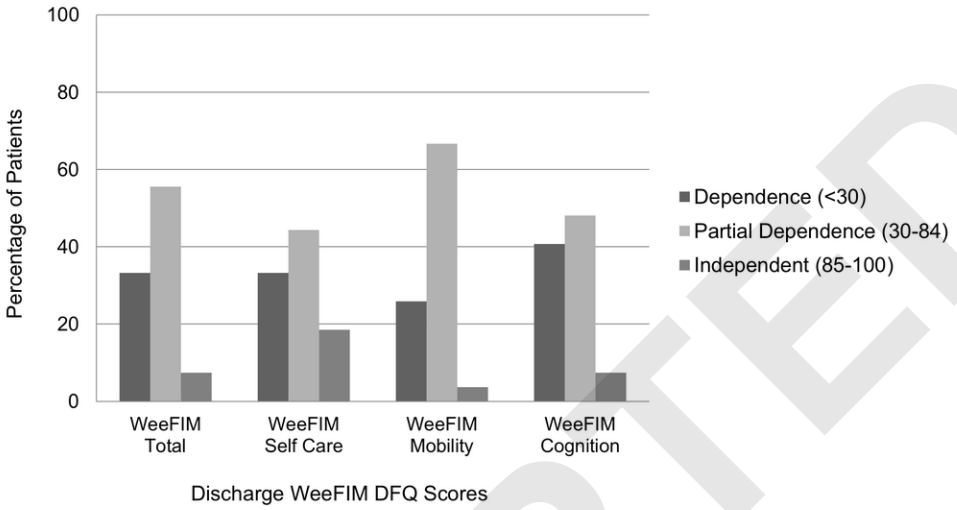


Figure 2



	n	(%)		
Gender				
Male	10	(37)		
Female	17	(63)		
Ethnicity				
Caucasian	7	(26)		
African American	17	(63)		
Hispanic	3	(11)		
			Mean	**Range**
Age at Symptom onset (years)			10.6	2-18
Time to First Line Tx (days)			27.2	5-91
Length of Stay (LOS; days)			39.0	14-108

	Normal		Abnormal	
	n	(%)	n	(%)
Initial MRI	22	(81.5)	4	(14.8)
EEG	8	(29.6)	19	(70.4)
LP/CSF	5	(18.5)	22	(81.5)
Serum	6	(22.2)	21	(77.8)
Teratoma	23	(85.2)	4	(14.8)

	n	(%)
First Line Treatments		
Steroid	24	(88.9)
IVIG	25	(92.6)
PLEX	12	(44.4)
Second Line Treatments		
Rituximab	19	(70.4)
Cyclophosphamide	4	(14.8)
Number of Treatments Received		
1-2	6	(22.2)
3	12	(44.4)
4-5	9	(33.3)