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Chronic Neurological Complications in Hemolytic Uremic Syndrome in Children

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Original Paper

Introduction. Central nervous system (CNS) involvement is the most common extrarenal involvement in hemolytic uremic syndrome (HUS). There are limited reports on clinical cause of chronic neurologic problems in HUS. We evaluated residual neurologic involvement in children with HUS.

Materials and Methods. This cross-sectional study was conducted on 58 patients with a diagnosis of HUS referred to 2 tertiary pediatric centers. Neurological examinations was performed on all of the patients and they were followed up between 2001 and 2015. Data including demographic variables, type of HUS, neurological symptoms, and other complications were recorded. Neurological involvements that occurred after 6 months from the acute phase of HUS were considered as chronic neurological involvement.

Results. Among 58 patients who were included in the study, 31 (53.4%) had neurological manifestations (31 with acute and 19 with chronic complications). There was no significant difference in acute neurological manifestations between typical and atypical HUS, while chronic neurological manifestations were more frequents in patients with atypical HUS (P = .05). The most common presentations were seizure and decreased level of consciousness. Chronic neurologic problems were found in follow-up visits of 11 patients with acute and 8 without acute involvement. Hypertension was associated with chronic manifestations (P = .01).

Conclusions. According to our results, residual neurological problems were not infrequent in HUS and they were more related with atypical form of disease. Evidence of hypertension is a significant variable for persistence of neurologic problems.

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INTRODUCTION

One of the most common reason of acute kidney injury in children is hemolytic uremic syndrome (HUS), and it is described as the condition of hemolytic anemia, thrombocytopenia, and acute kidney injury.[1,2] Diarrhea-associated or typical HUS is the most common type of this syndrome; that is commonly due to Shiga toxin produced by *Escherichia coli*.[1,3,4] In addition, some diseases and conditions like infection, malignancy, taking medications, and genetic problems can cause HUS, namely atypical type.[4]

The most common extrarenal involvement in HUS patients is central nervous system (CNS) involvement.[5] In the acute phase of disease, neurological symptoms (irritability, drowsiness, coma, cortical blindness, stroke, intracranial hemorrhage, ataxia, and tremor) are seen commonly

in patients along with other symptoms.[1,6-9] The most common acute neurologic problem is seizure.[6] Although, in long-term follow-up of patients with HUS, some problems like epilepsy, hemiparesis, neurodevelopmental delay, and cognitive defects could be find.[9] These CNS involvements are associated with morbidity and mortality in HUS patients.[5,10] Furthermore, early involvement of the nervous system is associated with chronic complications of the nervous system.[7] There are only a few reports on the clinical course of CNS problems in HUS and data on follow-up are limited. We conducted this study to evaluate the chronic CNS problems in children with HUS.

MATERIALS AND METHODS

In this multicenter cross-sectional study, the hospitals records of 58 patients with the diagnosis of HUS who were admitted into the two tertiary pediatric centers from 2001 to 2015, were collected. The diagnosis of HUS was determined according to the other studies, as the triad of acute kidney injury (creatinine more than normal range for age), hemolytic microangiopathic anemia (red cell fragmentation confirmed by a hematologist with a hemoglobin level less than 10 g/dL), and thrombocytopenia (platelet count less than 150 × 10^9/L).[1] Demographic data, type of HUS (diarrhea-associated is called typical and nondiarrhea-associated is called atypical), neurologic symptoms and result of neurologic examination during the acute phase of disease and some other complications such as hypertension and outcome of renal disease were extracted.

Prospective follow-up assessments were done for all patients. In this way, they announced to come to neurology clinic for taking comprehensive history and doing neurological examination by a pediatric neurologist. The neurological symptoms in the period prior to HUS and during the follow-up period were asked. Patients with recurrent HUS were considered as atypical HUS. All the CNS problems or new neurological manifestations that occurred after 6 months from the acute illness of HUS, considered as chronic neurologic involvement. Informed consent was obtained from the parents and ethics committee approved the study.

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, Chicago, IL, USA). Quantitative variables were expressed as the mean ± standard deviation. Analytical tests including the *t* test, Pearson chi-square test, Fisher test, and 1-way analysis of variance were used. Results were considered significant at a *P* value less than .05.

RESULTS

The medical records of 58 patients were analyzed. Thirty-three (56.9%) were males and 25 (43.1%) were females. The mean age was 3.9 ± 2.86 years old (range, 4 months to 14 years old). Twenty-six (44.8%) of all patients had been diagnosed as typical and 32 (55.2%) as atypical HUS. From the patients with CNS involvement, 12 patients (38.7%) had acute CNS involvement that 8 (66.7%) were females. Central nervous system manifestations were seizure, decreased level of consciousness, headache, hemiparesis due to acute stroke, and visual disturbances in order of frequency. No significant differences were seen in age and sex between patients with and without CNS manifestations. The main clinical data in children with acute phase and chronic phase are presented in Table 1.

Table 1. Demographic and Clinical Data of Children With Hemolytic Uremic Syndrome (HUS)

Characteristic	Acute Phase (HUSn = 39)	Chronic Phase (n = 19)	*P*
Age, y	2.7	4.9	.17
Sex			
Male	20	13	
Female	19	6	.17
Need to dialysis	23 (67.6)	11 (32.4)	.58
Admission to pediatric intensive care unit	10 (62.5)	6 (37.5)	.43
Hypertension	9 (52.9)	8 (47.1)	.12
Typical HUS	18 (69.2)	8 (30.8)	.50
Atypical HUS	21 (65.6)	11 (34.4)	.50
Mortality	7 (87.5)	1 (12.5)	.25

Persistence of neurological problems in follow-up visits were seen in 11 (91.7%) of the patients with acute CNS involvement. These included microcephaly, neurodevelopmental delay, movement disorders such as tremor, hemiparesis, visual problems (strabismus, blindness), speech delay, hydrocephalus and neurocognitive or neuropsychological problems such as reduced academic performance, depression, and aggression. Surprisingly, 8 patients (25.8%) without CNS involvement in acute phase, showed neurologic complications in follow-up visits including developmental delay, microcephaly, psychologic symptoms. Totally, in chronic phase, CNS involvement was seen in 19 patients (6 females and 13 males) that was not significant in the view of sex (P = .10). In patients with CNS complications, 8 patients (25.8%) had hypertension that in 5 patients (16.1%) hypertension had been started from acute illness phase and in 3 patients (9.7%) started later at follow-up visits (P = .01).

Overall, 19 (61.3%) of patients with CNS involvement needed to dialysis, including 6 (42.1%) in acute phase, 5 (26.3%) in chronic phase, and in 6 (31.6%) dialysis had been started from acute phase and then continued until follow-up visits (P = .32). Chronic CNS involvement was seen more frequent in patients with atypical comparing typical HUS (P = .05). On the other hand, in patients with acute CNS manifestations, typical or atypical HUS had no significant difference. Totally, 8 patients (13.8%) with HUS died (7 patients in acute phase and 1 patient in chronic phase), that 3 of them had CNS involvement. The relationship between some clinical variable in acute phase CNS involvement and having neurological involvement in chronic phase, also were evaluated. No significant differences were seen except for hypertension that was significantly related to presence of neurologic sign and symptoms in chronic phase (P = .01; Table 2).

DISCUSSION

Hemolytic uremic syndrome, especially Shiga toxin produced by *Escherichia coli*-HUS, could be a life threatening disease despite significant improvements in the management of patients. Central nervous system complications are the most frequent extrarenal involvement and is related to high mortality and morbidity.[1] However, the CNS involvement is usually reversible.[7,11] We observed neurologic involvement in 38.7% of patients with HUS. The most common manifestations were seizure and decreased level of consciousness and in 19 patients neurologic problems were seen in chronic phase. These data are similar to Sheth and colleagues' study. They reported 34% neurologic involvement among 44 children with HUS at Milwaukee Children's Hospital.[12] In their study, 6 of 15 patients demonstrated residual neurologic symptoms and in those with CNS involvement the incidence of residual hypertension, chronic renal damage and death was higher. In Bauer and colleagues' study on 50 patients with HUS, CNS manifestations were about 28% and all the patients when reached to chronic phase had complete neurologic recovery.[1] They did not report any chronic neurological problem. Martines and coworkers showed residual neurologic problems in 20% of patients with acute neurologic manifestations.[9] They reported brain lesions may persist despite clinical improvement. In our study, 8 patients died in acute phase of HUS that 3 of them had CNS involvement. While, in Nathanson and coworkers' multicenter study on 52 patients

Table 2. Relationship Between Clinical Parameters of Patients With Central Nervous System Involvement in Acute and Chronic Phases of Hemolytic Uremic Syndrome (HUS)

Parameter	Acute Phase (HUSn = 12)	Chronic Phase (n = 19)	*P*
Sex			
Male	4	13	
Female	8	6	.10
Need for dialysis	8	11	.36
Admission to pediatric intensive care unit	6	6	.32
Hypertension	0	8	.01
Typical HUS	8	8	.05
Atypical HUS	4	11	.05
Mortality	2	1	.77

with typical HUS and CNS involvement, mortality was reported in 17% and severe morbidity in 23% of patients.[13] In their study, coma, seizure, and pyramidal syndromes were the most common presentations and 50% of patients had complete neurologic recovery. They showed no relationship between the CNS involvement and mortality or morbidity. These results are different with ours because the study by Nathanson and colleagues did not enroll the patients with typical HUS in their study.

In our study, CNS problems in chronic phase were more frequent in atypical HUS. Although, it was not statistically significant. Genetic disorders of complement system or other underlying diseases in atypical HUS may be the reason for more frequency of neurologic problems. Multiple factors in HUS are responsible for CNS including local microangiopathy hyponatremia and hypertension.[13] We found a significant association between persistent hypertension and the acute or chronic CNS involvement that was similar to Sheth and colleagues' study.[12] Tavasoli and colleagues, in an unpublished systematic review regarding chronic neurological involvement in patients with HUS, found that the emergence of seizure in the acute phase of typical HUS can predict the neurologic outcome in follow-up (relative risk,1.56; 95% confidence interval, 0.91 to 2.66).[14]

A limitation of our study was the lack of neurophysiologic and neuroimaging studies for patients that could define the extent of CNS lesion. Therefore, we recommend conducting prospective studies in this regard in the future.

CONCLUSIONS

Our study showed neurologic involvement in patients with HUS could be persistent. These sequela were significantly related to hypertension in acute phase of HUS. Some patients without CNS involvement in acute phase of HUS showed neurologic problems later in follow-up visits, such as developmental delay or cognitive disturbances. Therefore, it is important to focus on taking precise history and doing neurologic examination at follow-up visits in HUS patients including those without CNS problems in acute phase of illness.

CONFLICT OF INTEREST

None declared.

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