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Frequency of neurological involvement in patients with/without diarrhea hemolytic uremic syndrome: A Systematic review and meta-analysis

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Abstract

Background: Diarrhea-associated-hemolytic-uremic-syndrome (D+HUS) is a common from of HUS. Central-nervous-system (CNS) involvement is one of the most common extrarenal organ involvements in children with D+HUS. This systematic review and meta-analysis aim to recognize the frequency of neurological complications in pts with HUS.

Methods: Databases of PubMed, Embase, and Web of Science were searched systematically to find the papers on neurological involvement in HUS pts. Two researchers independently assessed the papers' quality and extracted data. CMA v. 2.2.064. was used for data analysis. Heterogeneity was evaluated using the I-squared (I2) test, and a fixed/random-effects model was used when appropriate.

Results: In this review, 21 studies including 2,189 participants with a median age between 1.3-40-year-old, entered the meta-analysis. The meta-analysis in D+HUS patients indicated 27.0% with neurological complications (95% CI, 22.0%-32.6%), 25.5% of symptoms weren't categorized (95% CI, 15.9%-38.3%), 20.8% of them developed the seizures (95% CI, 2.3%-74.4%). In D-HUS pts, 20.8% of them were presented neurological symptoms (95% CI, 17.9%-24.0%), of which 29.0% weren't categorized (95% CI, 19.2%-41.2%), 17.5% of pts got into coma (95% CI, 9.6%-29.7%), 5.6 % showed hemiparesis (95% CI, 2.8%-10.9%), 17.2% experienced lethargy (95% CI, 5.2%-44.1%), 30.5% developed the seizures (95% CI, 18.2%-46.2%), 7.4% manifested speech abnormalities (95% CI, 0.2%-7.22%), 6.4% of D-HUS pts presented visual-disturbances (95% CI, 3.4%-11.6%).

Conclusion: This systematic review and meta-analysis indicated more than one-fourth of both D+HUS and D-HUS patients were presented with neurological symptoms, and the most prevalent symptoms were seizures, which can lead to an epilepsy sequel.

Keywords: HUS, CNS, Diarrhea, Neurological symptoms, Pediatrics, Adults

Conflicts of Interest: *None declared.*
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Introduction

Hemolytic–uremic syndrome (HUS) is a group of hemolytic disorders introduced by Gasser et al. (1) in 1995 and considered by low red blood cells and platelets, as well as acute kidney injury (2). HUS's initial symptoms include bloody and/or watery diarrhea, fever, vomiting, and fatigue (1, 2). Following initial symptoms, decreases in platelet levels and ki dney failure would occur (2). Although HUS mainly affects the children at pre-school age, outcomes are more critical in adults with the development of neurological sequels and heart failure (2).

Diarrhea-associated hemolytic uremic syndrome (D^+HUS) is the most common form of HUS, which includes almost 90% of HUS patients and leads to acute renal failure (ARF) in children under five years (3, 4). The leading cause of D^+HUS is Shiga-like toxin infection producing by Escherichia coli (E. coli) bacterium (mostly

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↑What is "already known" in this topic:
It is about the importance of CNS complications in HUS disease.

→What this article adds:
This article adds to our previous known knowledge that is the Neurologic complications should be monitored in all types of HUS in adults and children. The most common presentation of neurologic complications is a seizure that can lead to epilepsy.

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O157:H7 type) (5). The HUS type that does not associate with diarrhea (D^-HUS), mostly cases by Streptococcus pneumoniae infection, and atypical HUS (aHUS) are associated with inherited vs. non-inherited complement regulation disorders (5). One of the long-term complications of HUS is renal problems. In this case, a meta-analysis of Garg et al. indicated 12% of end-stage renal disease (ESRD) or death in D^+HUS cases and 25% long-term renal disorders (6). Although neurological involvements are not as common as renal disorders, central nervous system (CNS) involvement is the primary cause of death in D^+HUS patients (7, 8).

Hence, due to the lack of comprehensive study on the frequency of neurological complications, this study aims to use meta-analysis to regulate numerical data reported in the literature to quantify the burden of the matter better and integrate what is already known.

Methods

Study Design & Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used for providing different steps of the study. Databases of PubMed, Embase and Web of Science were searched systematically up to June 28, 2020. The search strategy included all MeSH terms and free keywords found for "Hemolytic Uremic Syndrome, "sequel*", and "neurology*" as follows: ("Hemolytic Uremic Syndrome" OR "Hemolytic-Uremic" OR "Gasser's Syndrome" OR "Gassers Syndrome" OR "Gasser Syndrome" OR "Hemolytic-Uremic Syndrome") AND ("associated disease" OR sequelae OR sequels OR "coexistent disease" OR "concomitant disease" OR "associated conditions" OR "coexistent conditions" OR "concomitant conditions" OR complications) AND (Neurological OR Neurology). The search was limited to English studies, but there were no time and location limitations in this regard.

Inclusion and exclusion criteria

Studies comprised of meta-analysis: comparative/non-comparative studies with retrospective/prospective nature, which reported the neurological complications in HUS patients. In vitro studies, experimental studies, reviews, case reports, and duplicate publications were excluded.

Data extraction & quality assessment

Variables such as first author name, year of publication, study region, study design, number of patients, age, neurological complications, mean age, follow-up duration, and mortality. For quality assessment, the modified Newcastle-Ottawa Scale (NOS) was used.

Data analysis

Comprehensive Meta-Analysis (CMA) v. 2.2.064 software was used for statistical analysis. The I-square (I^2) test was used for the heterogeneities assessment. The pooling of effect sizes was done with 95% Confident Interval (CI). According to the study's heterogeneity, a fixed-effects/random-effects model was used as appropriate for heterogeneity more/less than 50%, respectively.

Publication bias

Begg's and Egger's tests were performed to evaluate publication bias, and the funnel plot has presented. A P-value of less than 0.05 was measured as statistically significant.

Results

Study selection & characteristics

The initial database search resulted in 926 papers. After duplicated publication removal and title/abstract screening step, 114 papers were included in the eligibility assessment step. Finally, 22 papers entered into the qualitative synthesis, of which 21 papers entered the meta-analysis.

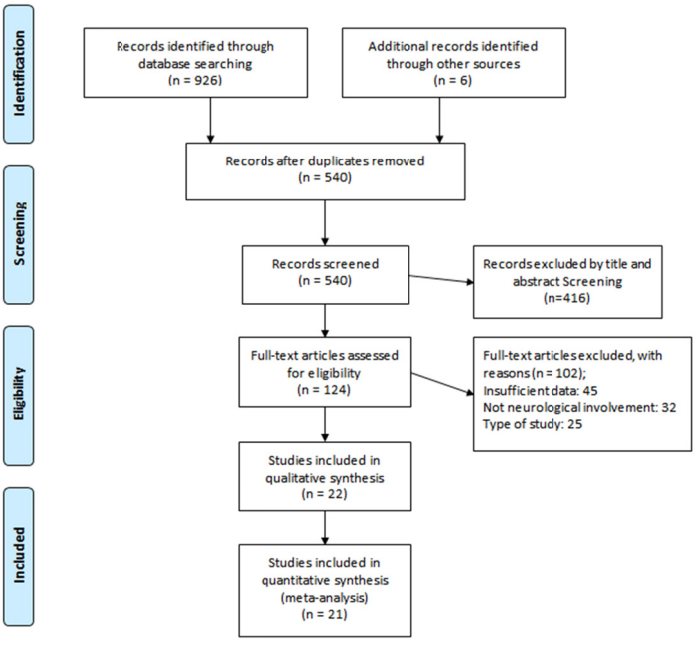

Fig. 1. PRISMA Flow-chart for the study selection process

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Table 1. Characteristics of studies included in the systematic review

Study	Country	Study design	No. of Patients (male/female)	Age, median (IQR)	Neurological Signs and symptoms		Neurological squeals	EEG	Duration of study	Death
					Diarrhea$^-$ HUS Patients	Diarrhea$^+$ HUS Patients				
Elzouki et al. (1995) (9)	Saudi Arabia	RCS	28 (14/14)	2.2	-	Neurologic complications: 11	-	-	15 months	-
Qamar et al. (1996) (10)	Canada	RCS	7 (3/4)	2.4	Seizure: 7 Irritability: 2 Delirium: 1		-	Normal: 2 Abnormal: 2 No-reported: 3	6 years	1
Cimolai et al. (1998) (11)	Canada	RCS	51	-	-	Neurological complications: 11 Encephalopathy: 6 Seizure: 7	-	-	11 years	2
Schlieper et al. (1999) (12)	Canada	RCS	205	8.6	Lethargy: 58 Seizures: 9 Coma: 1	-	-	-	3 year	-
Eriksson et al. (2001) (13)	UK	RCS	22 (11/11)	3.3	Coma: 9 Seizures: 14	-	Epilepsy: 2 Dysphasia: 1 Visual problem: 2 Homonymous hemianopia: 1 Cognitive deficit: 1	Early EEG Slow: 17 Periodic: 5	7 years	5
Yamamoto et al. (2009) (14)	Japan	RCS	71 (27/44)	-	-	Lethargy: 7 Headache: 1	-	-	-	-
Nathanson et al. (2010) (15)	France	RCS	52	-	-	Alteration in consciousness: 44 Seizures: 37 Pyramidal syndrome: 27 Pyramidal syndrome with hypertonia: 22 Coma and seizures in addition to pyramidal and extrapyramidal syndromes: 12	Hemiparesia:3 Dystonia: 1 Ataxia: 1 Dysphasia: 1 Epilepsy: 2 Tetraparesia: 1 Blindness: 1 Pyramidal: 1 Claude Bernard Horner: 1 Visual defect: 1 Developmental delay: 1 Severe disability: 5	-	33 years	9

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de Souza et al. (2011) (16)	Brazil	Prospective cohort	13 (5/8)	3.2	Neurological symptoms: 4	-	-	-	5 years	-
Loos et al. (2012) (17)	Germany	RCS	90 (41/49)	11.5	Neurological Symptoms: 23 • Seizures: 16/23 • Impaired consciousness • Including coma: 17/23 • Visual disturbances: 7/23	-	-	-	3 months	1
Rosales et al. (2012) (18)	Germany	RCS	690	2.9	Seizures, coma, stroke, and severely retarded motor development	-	-	-	6 years	7
Ekinci et al. (2013) (19)	Turkey	RCS	70 (33/37)	7.07	CNS involvement: 15	-	-	-	-	3
Braune et al. (2013) (20)	Germany	RCS	106 (24/82)	40 (18–83)	Severe neurological symptoms and signs: 70 Cognitive dysfunction: 39 Aphasia: 31 Epileptic seizures: 31 Myoclonus: 25	-	-	-	4 months	5
Bauer et al. (2014) (21)	Germany	RCS	50 (23/27)	11.9	Neurological involvement: 14 • Seizure: 11/14 • Impaired consciousness: 11/14 • Visual disturbances: 4/14 • Myocloni: 3/14 • Hemiparesis: 2/14	-	Hemiparesis: 1	Abnormal: 25/39 Slowing of background activity: 21/39 Focal slowing: 5/39 Epileptic discharges: 5/39	1 year	1

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					Diarrhea$^-$ HUS Patients	Diarrhea$^+$ HUS Patients				
Buder et al. (2015) (22)	Germany	Retrospective cohort	16* (6/10)	1.3 (0.3–14.4)	Seizures: 12/16 Isolated seizures: 5/16 Altered consciousness: 7/16 Isolated altered consciousness: 2/16 Ataxia: 4/16 Muscle tone abnormality: 2/16 Hemiplegic symptoms: 2/16 Dysarthria: 1/16 Visual disorders: 1/16 Movement disorders: 2/16 Vestibular symptoms: 1/16 >1 neurological symptom: 8/16 Number of neurological symptoms: 1: 8/16 2: 5/16 3: 0/16 4: 1/16 5: 2/16	-	-	-	1 year	-
Jenssen et al. (2016) (23)	Norway	RCS	47 (16/31)	2	Neurological complications: 2	Neurological complications: 9	-	-	10 years	2
Durkan et al. (2016) (24)	Australia	Prospective cohort	122 (65/57)	2.9	Neurological involvement: 23	-	-	-	8 years	-
Şahin et al. (2017) (25)	Turkey	RCS	64	-	Neurological involvement: 24 Seizure: 15 Headache: 6 Motor paresis with pyramidal tract signs: 6 Alteration of consciousness: 5 Sensory symptoms: 3	-	-	Abnormal: 7/13 Slow-wave: 4/13 Epileptiform abnormalities: 2/13	10 years	6
Loos et al. (2017) (26)	Germany	RCS	72	11.55	Neurological symptoms: 19	-	-	-	1 year	1

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					Diarrhea$^-$ HUS Patients	Diarrhea$^+$ HUS Patients				
Karnisova et al. (2018) (27)	Czech Republic	RCS	33 (18/15)	2.4	-	Impaired consciousness: 4 Seizures: 1 Paleocerebellar syndrome: 2 Quadriparesis: 1 Cranial nerve palsy: 2 Hallucinations: 1	-	-	16 years	-
Clech et al. (2019) (28)	France	RCS	235	-	Neurologic involvement: 30	-	-	-	18 years	-
Tavasoli et al. (2019) (29)	Iran	RCS	58	3.4	CNS involvement: 31	-	-	-	14 years	8
Ylinen et al. (2020) (30)	Finland	RCS	87	-	Seizures: 24 Impaired consciousness: 15 Hemiparesis: 4 Minor CNS symptoms: 12 Lethargy: 8 Irritability: 2 Vision abnormality: 1 Speech abnormality: 1 Fluctuating hemiparesis: 1	-	-	-	15 years	-

HUS: Hemolytic-uremic syndrome, IQR: Interquartile range, EEG: Electroencephalography UK: United Kingdom, RCS: retrospective cross-sectional
* patients with CNS involvement during acute episode of HUS

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PRISMA flow diagram for the study selection process is presented in Figure 1. The sample size of studies included in the systematic review ranged from 7 to 690, including 2,189 participants with a median age between 1.3 to 40 years old. Characteristics of studies included in the systematic review presented in Table 1.

Quality assessment

Results of the quality assessment for studies entered into meta-analysis based on a modified version of the NOS tool for cross-sectional studies were fair.

Publication bias

Begg's and Egger's tests in effect size meta-analysis showed no significant publication bias for both D^+HUS patients (P_B=0.60; P_E=0.54) and D^-HUS patients (P_B=0.78; P_E=0.77). The funnel plot for publication bias of studies presented in Figure 2.

Meta-analysis findings

The meta-analysis of event rates in D^+HUS patients indicated that 27.0% of such patients manifested neurological complications (95% CI, 22.0%-32.6%), of which 25.5% of symptoms were not categorized (95% CI, 15.9%-38.3%), and 20.8% of such patients developed the seizures (95% CI, 2.3%-74.4%). Other neurological symptoms that only reported in single studies were alteration in conciseness (84.6%), coma (12.1%), cranial nerve palsy (6.1%), encephalopathy (11.8%), hallucinations (3.0%), headache (1.4%), lethargy (9.9%), paleocerebellar syndrome (6.1%), pyramidal syndrome (51.9%), and quadriparesis (3.0%) (Fig. 3).

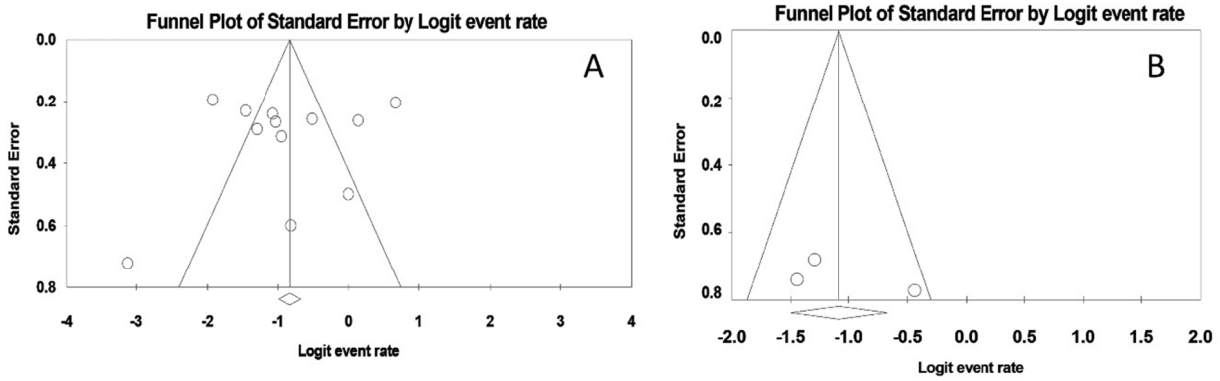

Fig. 2. Funnel plot for publication bias; (A): D^-HUS patients, (B): D^+HUS patients

Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study: Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total
Alteration in consciousness	Kamisova 2018	Alteration in consciousness	0.846	0.721	0.921	4.435	0.000	44 / 52
Alteration in consciousness			0.846	0.721	0.921	4.435	0.000	
Coma	Kamisova 2018	Coma	0.121	0.046	0.282	-3.714	0.000	4 / 33
Coma			0.121	0.046	0.282	-3.714	0.000	
Cranial nerve palsy	Kamisova 2018	Cranial nerve palsy	0.061	0.015	0.212	-3.757	0.000	2 / 33
Cranial nerve palsy			0.061	0.015	0.212	-3.757	0.000	
Encephalopathy	Cimolai 1998	Encephalopathy	0.118	0.054	0.238	-4.636	0.000	6 / 51
Encephalopathy			0.118	0.054	0.238	-4.636	0.000	
Hallucinations	Kamisova 2018	Hallucinations	0.030	0.004	0.186	-3.413	0.001	1 / 33
Hallucinations			0.030	0.004	0.186	-3.413	0.001	
Headache	Yamamoto 2009	Headache	0.014	0.002	0.093	-4.218	0.000	1 / 71
Headache			0.014	0.002	0.093	-4.218	0.000	
Lethargy	Yamamoto 2009	Lethargy	0.099	0.048	0.193	-5.559	0.000	7 / 71
Lethargy			0.099	0.048	0.193	-5.559	0.000	
Neurological symptoms	Cimolai 1998	Neurological symptoms	0.216	0.124	0.349	-3.792	0.000	11 / 51
Neurological symptoms	Elzouki 1995	Neurological symptoms	0.393	0.233	0.580	-1.125	0.261	11 / 28
Neurological symptoms	Jenssen 2016	Neurological symptoms	0.191	0.103	0.329	-3.885	0.000	9 / 47
Neurological symptoms			0.255	0.159	0.383	-3.542	0.000	
Paleocerebellar syndrome	Kamisova 2018	Paleocerebellar syndrome	0.061	0.015	0.212	-3.757	0.000	2 / 33
Paleocerebellar syndrome			0.061	0.015	0.212	-3.757	0.000	
Pyramidal syndrome	Nathanson 2010	Pyramidal syndrome	0.519	0.385	0.650	0.277	0.782	27 / 52
Pyramidal syndrome			0.519	0.385	0.650	0.277	0.782	
Quadriparesis	Kamisova 2018	Quadriparesis	0.030	0.004	0.186	-3.413	0.001	1 / 33
Quadriparesis			0.030	0.004	0.186	-3.413	0.001	
Seizure	Cimolai 1998	Seizure	0.137	0.067	0.261	-4.518	0.000	7 / 51
Seizure	Kamisova 2018	Seizure	0.030	0.004	0.186	-3.413	0.001	1 / 33
Seizure	Nathanson 2010	Seizure	0.712	0.575	0.818	2.950	0.003	37 / 52
Seizure			0.208	0.023	0.744	-1.090	0.276	
Overall			0.270	0.220	0.326	-7.251	0.000	

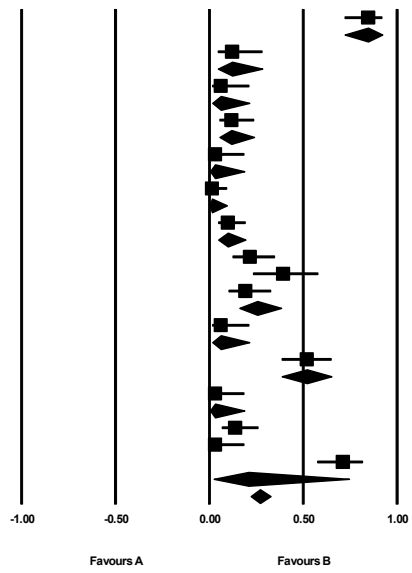

Fig. 3. Frequency of neurological symptoms in D^+HUS patients

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Among D⁻HUS patients, 20.8% of them were presented neurological symptoms (95% CI, 17.9%-24.0%), of which 29.0% of patients' symptoms were not categorized (95% CI, 19.2%-41.2%), 17.5% of patients got into coma (95% CI, 9.6%-29.7%), 5.6 % showed hemiparesis (95% CI, 2.8%-10.9%), 17.2% experienced lethargy (95% CI, 5.2%-44.1%), 30.5% developed the seizures (95% CI, 18.2%-46.2%), 7.4% manifested speech abnormalities (95% CI, 0.2%-7.22%), and 6.4% of D⁻HUS patients presented visual disturbances (95% CI, 3.4%-11.6%). Other neurological symptoms that only reported in single studies were aphasia (29.2%), ataxia (25.0%), cognitive dysfunction (36.8%), delirium (14.3%), headache (9.4%), and irritability (28.6%), and motor paresis (9.4%) (Fig. 4).

In total, 24.4% of HUS patients with/without diarrhea were presented neurological symptoms (95% CI, 21.6%-27.5%) (Fig. 5).

Discussion

The most studied subject on HUS patients has focused on renal problems (6, 31). There are a few well-organized studies with long-term follow-up, which considered the neurodevelopmental complications among such patients. Also, to our knowledge, there is no systematic review and meta-analysis on the subject. Hence, we have gathered all available data on the issue, which only resulted in descriptive outcomes due to the limited information.

We found that more than one-fourth of D⁺HUS patients were presented neurological symptoms, and the most prevalent symptoms were seizures, which led to epilepsy sequel in some cases that only reported in two studies (13, 15). Other neurological symptoms that were reported include alteration in conciseness, coma, cranial nerve palsy, encephalopathy, hallucinations, headache, lethargy, paleocerebellar syndrome, pyramidal syndrome, and quadriparesis.

The hemolytic uremic syndrome is a multi-organ disease in which CNS involvement occurs in 20-50% of patients during the acute phase (32, 33). This comprehensive range of incidence may be due to the difficulty of diagnosis in the cases of minor CNS manifestations among these children. Regardless of renal involvement high frequency, CNS involvement is the main reason for mortality in Shiga like toxin-producing Escherichia coli (STEC) HUS patients. This fact indicates the microvascular damage in cerebral areas (7).

In in vitro studies, although HUS thrombotic microangiopathic (TMA) was observed in renal vessels, it was not

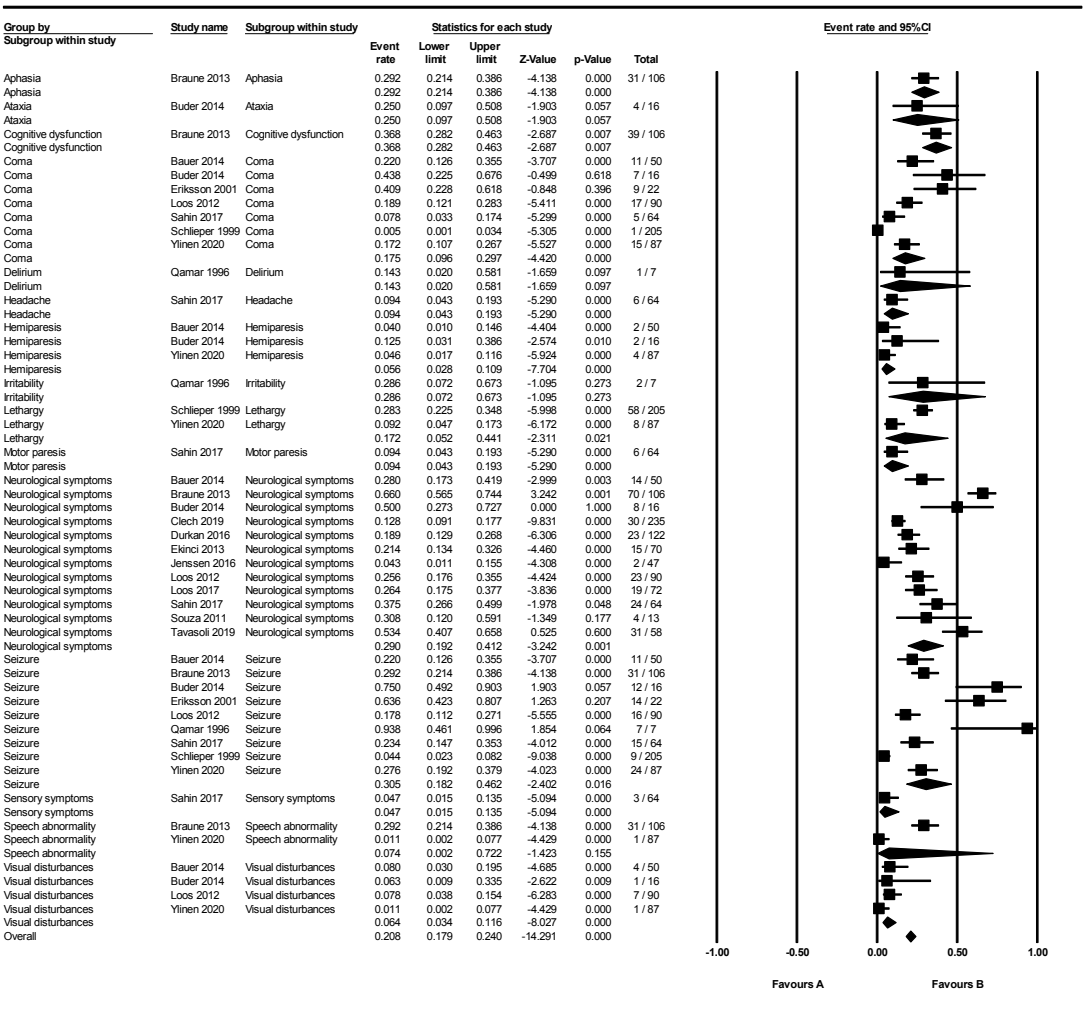

Fig. 4. Frequency of neurological symptoms in D⁻HUS patients

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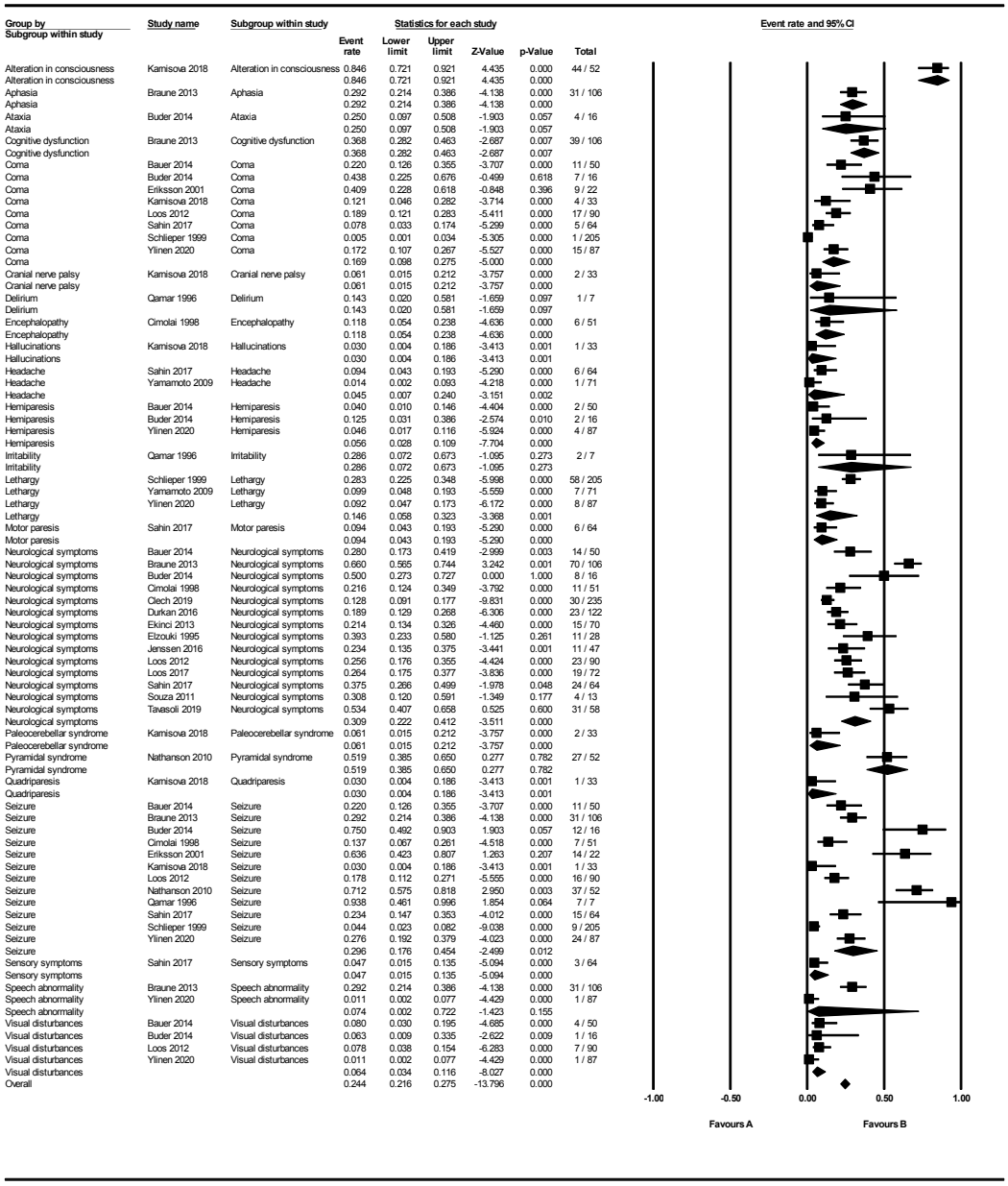

Fig. 5. Frequency of neurological symptoms in HUS patients with/without diarrhea

found in the brain's endothelium (34, 35). However, cerebral ischemia due to Shiga toxin was observed in rabbit models; also, arteriolar necrosis of the brain and endothelial cell damage was found in piglet models (36, 37). Hence, it can be concluded that various types of endothelium respond to Shiga toxin individually. In this regard, the sensitivity of human intestinal microvascular endothelial cells (HIMEC) to Shiga toxins is much more in comparison to human saphenous vein endothelial cells (HSVEC) (38).

Clinically and experimentally, neurological involvement is the deadliest complication of STEC-HUS. Common manifestations of CNS involvement include altered consciousness, irritability, seizure, coma, hemiparesis, ataxia, apnoea, blindness, varying degrees of encephalopathy, stroke, de-cerebration, and dystonic posture (5, 7). Causes of neurological involvement are multifactorial and may be due to generalized insult from metabolic disorders such as hyponatremia, hypocalcemia, and uremia, or due to hypertension. The direct effects of Shiga toxin on the brain's neuronal and endothelial cells may lead to hemorrhage or infarction. Some authors consider microangiopathy as the main cause of CNS involvement in $D^{+}HUS$ (39, 40). It has also been reported that antecedent enteritis associated with bloody diarrhea and gastrointestinal manifestations might be related to the severity of neurological involvement (7).

In the case of treatment for such patients, there is a lack of evidence-based guidelines. The study of Nathanson et al. (15) indicated promising effects of plasma exchange in HUS patients with critical CNS involvement. Also, the study of Dundas et al. on "Effectiveness of therapeutic plasma exchange in the 1996 Lanarkshire Escherichia coli

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O157:H7 outbreak" in Scotland demonstrated survival effects for plasmapheresis. In this study, although platelet counts recovered to the normal values during one week in 25% of patients, other patients showed no improvement with the approach. It has also been reported that plasma exchange deteriorated the renal function and increased the neurological complications as well as the dialysis need (8). Hence, plasmapheresis is not generally accepted as a practical approach to treating HUS patients with CNS involvement (41).

In the 2011 O104:H4 outbreak, monoclonal antibody eculizumab was used as a new approach to treating HUS patients with critical neurological involvement. This humanized anti-C5 monoclonal antibody inhibits the complement system and stops developing the terminal complement complex and is approved to be considered for the treatment of paroxysmal nocturnal hemoglobinuria (42). However, various data on the efficacy of the eculizumab demonstrates a wide range of treatment effects in different regions (17, 43).

According to the current systematic review and meta-analysis findings, due to the lack of well-organized guidelines and long-term studies on the HUS patients' neurological complications, diagnosis approaches, and treatment applications, further large long-term clinical trials should be taken into account to achieve more reliable findings.

It is worth mentioning that the current study includes several limitations: a) due to lack of long-term studies and analytical data, considering long-term sequels were not probable; b) small sample size of studies would lead to type II statistical errors.

Conclusion

This systematic review and meta-analysis indicated more than one-fourth of both D^+HUS and D^-HUS patients were presented with neurological symptoms. The most frequent symptoms were seizure development, which can potentially lead to epilepsy sequel. For overcoming the limitations, robustly long-term controlled randomized studies are recommended.

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Conflict of Interests

The authors declare that they have no competing interests.

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