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Original Research Article

Long-term follow-up of children with typical hemolytic uremic syndrome

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ABSTRACT

Objective: The aim of the study was to determine the associations of the acute period course with late-emerging sequelae in children with typical hemolytic uremic syndrome (HUS).

Materials and methods: The data of 62 children with typical HUS during the acute phase were retrospectively analyzed by age, sex, duration of anuria/oliguria, method and duration of renal replacement therapy, proteinuria, hypertension, and renal function. The data of 33 children at 10-year follow-up after the onset of the disease were evaluated for changes in hypertension, proteinuria, and renal function.

Results: In the acute phase of the disease ($n = 62$), hypertension was documented in 75.8% of the children; proteinuria, in 85.5%; and renal dysfunction, in 100%. At 10 years after the onset of the disease ($n = 33$), hypertension was documented in 12.1%, 6.1%, and 24.2% at 1-, 5-, and ≥ 10 -year follow-ups, respectively, and more often in children aged < 1 year at the onset of the disease. Proteinuria was found in 15.2%, 9.1%, and 33.3% of the patients, respectively. After ≥ 10 years, hypertension developed for the first time in 6.1% of the patients. Renal injury of varying degrees was seen in 15.2% of the children at the 1-year follow-up, and after ≥ 10 years the proportion increased to 33.3%.

Conclusions: At 10 years after the acute phase of typical HUS in children, the prevalence of hypertension and proteinuria at 1- and 5-year follow-ups decreased, but after 10 years it started to increase. As much as 6.1% of the children developed hypertension or proteinuria for the first time at 10 years. Hypertension was documented more frequently in children who were younger than < 1 year at the onset of the disease. Renal dysfunction after 5 and 10 years

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remained in more than one-third of cases, and it was observed more often if hypertension was documented at the acute period.

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1. Introduction

Hemolytic uremic syndrome (HUS) is the major cause of acute kidney injury, resulting in a mortality rate of 1%–10%. HUS causes chronic kidney disease in most patients [1–4]. In the acute phase, 50%–60% of children require renal replacement therapy (RRT). Anuria lasting for 5–14 days is associated with worse outcomes [5,6]. Diarrhea-associated (D+) HUS is more common (80%–90%) than atypical HUS and primarily affects young children (<5-year olds) [1,4,7]. In North America, D+ HUS is diagnosed in every 2–3 per 100,000 children; in Europe, 2 per 100,000 children younger than 5 years [8]. In Argentina, where D+ HUS is considered endemic, the incidence of the disease reaches 17 per 100,000 children aged <5 years [9]. During the acute phase of D+ HUS, 97% of the patients experience renal failure, 20% have seizures, and 47% have hypertension [1,10]. The prognosis and long-term outcome depend on the severity of the disease. Severity is determined by pyrexia >39 °C, leukocyte count of >20 × 10⁹ L⁻¹, anuria lasting for more than 8 days, need for RRT, age of <2 years, seizures and other involvement of the central nervous system [1,9,10]. From 5% to 12% of the children who have D+ HUS later develop end-stage kidney disease; 6%–30% have persistent proteinuria or hypertension [1,4,6,10]. Incidence rates, course of disease, models of clinical studies, and results of long-term follow-ups, vary being rather diverse among countries [4,9,11], and it is not known for how long children should be followed up after development of D+ HUS.

The aim of our study was to determine the associations of patient's age at the onset of the disease and severity of the acute phase with long-term outcomes and to identify the causes of persistent or late-emerging proteinuria, hypertension, and declining renal function.

2. Materials and methods

This retrospective clinical study included all children diagnosed with typical HUS and treated in two pediatric nephrology centers belonging to two university's hospitals (Hospital of Lithuanian University of Health Sciences Kauno Klinikos and Children's Hospital, an Affiliate of Vilnius University Hospital Santariškių Klinikos) during 1992–2013. Data were acquired from patients' medical documents; in all the cases, parental informed consent was obtained. The study received ethical approval. Data were evaluated during the acute phase of the disease and at 1 year, 5 years, and ≥10 years after onset. Diagnosis was based on clinical and laboratory data at hospitalization: diarrhea during previous 10 days, hemolytic anemia (Hb <100 g/L with microscopic evidence of fragmented erythrocytes), thrombocytopenia (platelet count

of <150 × 10⁹ L⁻¹), and acute renal failure (increased serum creatinine concentration above the upper reference limit for age). During the acute phase, age, sex, duration of anuria/oliguria, method and duration of RRT, season of onset, proteinuria, hypertension, central nervous system involvement, and renal function during hospitalization and at discharge from hospital were evaluated. For the follow-up visits, physical development, blood pressure (BP), renal function, and 24-h proteinuria were assessed. Proteinuria was defined as >0.2 g/L. Hypertension was defined as systolic or diastolic BP at the >95th percentile for age, sex, and height. Results were interpreted using standardized tables approved by the European Society of Hypertension [12]. We conducted 24-h BP monitoring at the 10-year follow-up to detect masked or nocturnal hypertension. The SCHILLER BR102 V2.4 monitoring system, programmed to measure BP every 30 min during daytime (from 6:00 AM to midday) and every 60 min during nighttime (from midnight to 6:00 AM) was used. Declined renal function was determined by an estimated glomerular filtration rate (eGFR) of <90 mL/min/1.73 m² according to the Haycock–Schwartz formula [13]. For the acute phase, we collected and analyzed the data of 62 children. For data at follow-up visits, because our study was retrospective, we analyzed the data in two groups since we could not collect the data of all children at all follow-up visits. In the first group, there were 38 children at follow-up visits at 1 and 5 years after the onset. In the second group, there were 33 children at follow-up visits after ≥10 years (5 children were excluded because 10 years did not pass from the onset of the disease).

2.1. Statistical analysis

The SPSS 19.0 statistical package was used to analyze the data. Continuous variables are expressed as mean and standard deviation. Differences between groups were assessed by the Student t and Mann–Whitney tests for continuous variables and the chi-square goodness-of-fit and interdependence tests for categorical values. Depending on the sample size, exact (for small size) and asymptomatic criteria were used. Changes in proteinuria, eGFR, and hypertension after 1, 5, and ≥10 years were estimated using the Wilcoxon and McNemar tests. Relative risk was estimated using Cox regression analysis. Statistical significance was assumed at a P value of <0.05.

3. Results

Based on the data from two pediatric nephrology centers in Lithuania, D+ HUS was diagnosed in 73 children during 1992–2013. Of these, 11 could not be contacted or were unable to attend follow-up visits for various reasons. A total of 62 pediatric patients were enrolled into the study, including 24

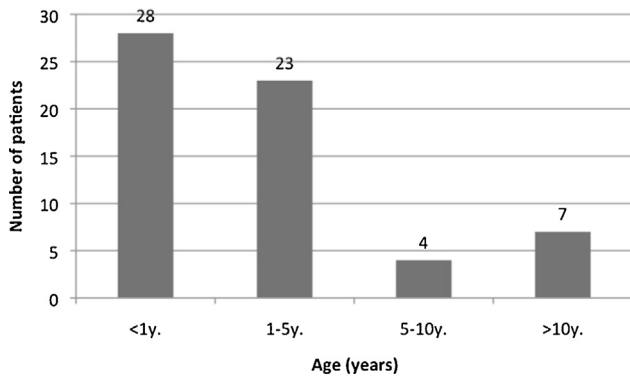


Fig. 1 – Distribution of patients during the acute period by age.

males (38.7%) and 38 females (61.3%). The mean time of follow-up was 12.4 ± 4.5 years (range, 6.2–18.9 years). The mean age at diagnosis was 2.9 ± 3.9 years (range, 0.3–14.3 years). Less than half (45.2%, 28/62) of the children were aged less than 1 year at the onset of the disease, and 82.3% (51/62) were younger than 5 years (Fig. 1). Data of 38 children were collected from follow-up visits at 1 and 5 years after the onset. Data of 33 children were collected after ≥ 10 years, as 10 years from the onset did not pass for 5 children. Distribution by age at diagnosis was the same in all follow-up groups. Less than half (15 of 33, 45.5%) of the children whose data were analyzed after ≥ 10 years were younger than 1 year and 84.8% (28 of 33) were younger than 5 years at the onset of the disease.

Seasonally, the onset of disease occurred significantly more often in spring and summer than in autumn and winter (66.1% vs. 33.9%, $P = 0.013$). Hypertension in the acute phase was observed in 75.8% (47/62), proteinuria in 85.5% (53/62), and renal dysfunction in 100% of the children. RRT (hemodialysis or peritoneal dialysis) was performed in 38 patients (61.3%).

In the first group of the children whose data were analyzed after 1 and 5 years, the proportions of the children with hypertension and proteinuria decreased to 18.4% (7/38) and 10.5% (4/38) and to 26.3% (10/38) and 7.9% (3/38), respectively (Fig. 2). After 1 and 5 years, renal dysfunction of various degrees was observed in 26.3% and 39.5%, respectively (Fig. 2). There was no significant difference in renal injury after 1, 5,

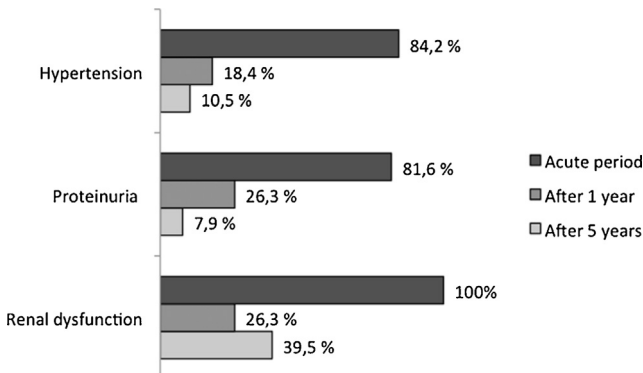


Fig. 2 – Dynamics of residual symptoms of HUS in group of children after 5 years follow-up (n = 38).

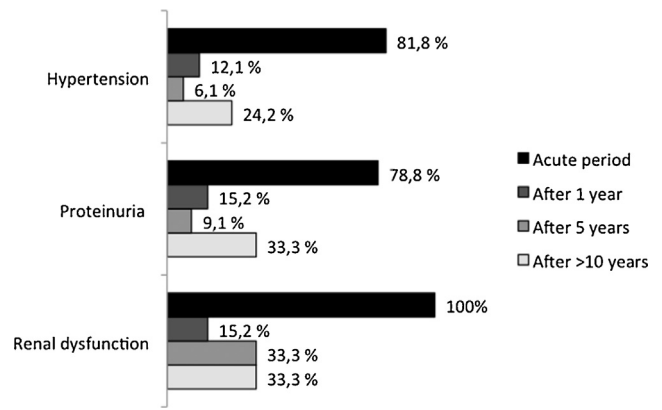


Fig. 3 – Dynamics of residual symptoms of HUS in group of children after 10-year follow-up (n = 33).

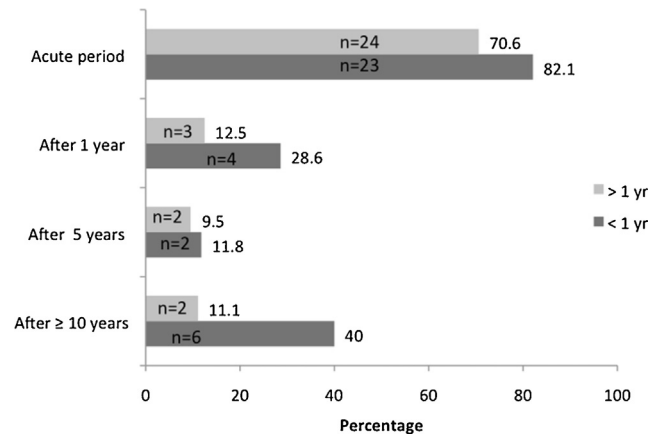


Fig. 4 – Frequency of hypertension in different periods of observation by age at onset (aged <1 year vs. aged >1 year).

and ≥ 10 years in the groups of children who were dialyzed for less than 7 days or more than 7 days.

Data from the second group ($n = 33$) showed that 12.1%, 6.1%, and 24.2% of the patients, had hypertension at 1, 5, and ≥ 10 years, respectively (Fig. 3). After ≥ 10 years of onset of the disease, hypertension was documented more often in those patients who were younger than 1 year in the acute phase of the disease (40% vs. 11.1%, $P = 0.05$) (Fig. 4). After ≥ 10 years, 6.1% (2 of 33) of patients developed hypertension for the first time without any signs of it in earlier follow-up periods. Comparison of the findings from the acute period with those at follow-up showed that the proportion of the children with proteinuria significantly decreased to 15.2% and 9.1% ($P = 0.001$) after 1 and 5 years, respectively (Fig. 3); however, 6.1% of the patients developed it for the first time at ≥ 10 years (Fig. 5). At the 1-year follow-up, renal injury of various degrees was observed in 15.2% of the children; however, after 5 and ≥ 10 years, it accounted for 33.3% (Fig. 3). The Cox regression analysis showed that children with hypertension at the onset of the disease were 24.39 times (95% CI, 2.14–278.20) more likely to have a decreased eGFR after ≥ 10 years ($P = 0.04$). After ≥ 10 years, end-stage kidney disease developed in 2 patients

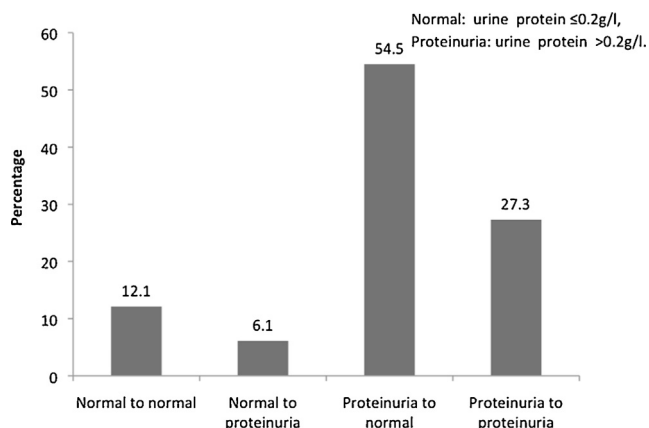


Fig. 5 – Changes of proteinuria at 10-year follow-up after onset (n = 33).

(6.1%), and both patients successfully underwent cadaveric renal transplantation. One-third (33.3%) of the children fully recovered after ≥10 years. Eight patients (10.9%) died in the acute phase of the disease; 5 (62.5%) of them were aged less than 1 year. The causes of death were cerebral hemorrhage, progressing cerebral edema, and massive intestinal necrosis.

4. Discussion

Numerous studies assessing long-term outcomes have reported the worst sequelae for children younger than 1 year at the onset of the disease. For 5%–15% of patients, hypertension persists after the acute phase [1,4,14]. In our study, hypertension in the acute phase was found in 75.8% of the children, and this percentage decreased to 10.5% after 5 years. Hypertension can also be masked in HUS patients, and conventional BP measurements may not be adequate. Krmar et al. [15] have shown in their study that 24-h BP monitoring is essential for evaluating hypertension. The data of 24-h BP monitoring were not available in our study for patients at 1- and 5-year follow-up visits, but monitoring was performed in all 33 children at the 10-year follow-up. We detected hypertension in 24.2% of the children: the same children who had hypertension using conventional BP measurements. Hypertension was observed more often in the patients aged <1 year at the onset of the disease (40% vs. 11.1%, $P = 0.05$). However, due to the small number of cases, we did not find a significant difference between conventional BP measurements and 24-h BP monitoring.

Proteinuria is considered a significant risk factor for progression to chronic kidney disease by many authors [2,6,10,17]. Proteinuria develops during follow-up in 15%–30% of D+ HUS patients [1–4]. In a study carried out in Argentina including 130 D+ HUS patients, microalbuminuria after 5 years was detected in 20.8% of the patients and proteinuria in 11.5% [16]. In our study, 85.5% of the children had proteinuria at the time of discharge, and this proportion decreased significantly after 1 and 5 years ($P = 0.001$) with only 7.9% of the patients having proteinuria after 5 years, but after 10 years it increased to 33.3%. Proteinuria persisted more often in children who

experienced it at the onset of the disease ($P = 0.01$). In the group of patients who did not have proteinuria in the acute period, 6.1% developed it after ≥10 years (Fig. 5). An increased percentage of patients with proteinuria was also found in a study of 208 children with D+ HUS by Repetto [10]: 6% after 1 year, 14% after 3 years, and 18% after ≥10 years.

More than half (50%–69%) of patients require RRT during the acute phase of the disease [3,4,11,18]. RRT was applied to 61.3% of the acute patients in this study. Since D+ HUS is more common in young children, priority is generally given to peritoneal dialysis. Some authors [1,10,14] state that RRT for more than 7 days is a risk factor for a worse outcome. Complete recovery of renal function is less frequent for those patients who required RRT for 4 weeks [1]. Lorait concluded that 30% of the patients had kidney injuries of various degrees following the application of RRT [18]. Rosales et al. [3] reported that patients who were dialyzed for more than 15 days expressed more symptoms of kidney injury. Our data did not show that the application of RRT or its duration had a negative influence on the emergence of hypertension or proteinuria and progression of renal failure. Our results showed that the longer time after the disease increased both the likelihood of chronic kidney injury development and degree of progression of the injury. Some authors report that chronic renal failure occurs approximately after 8–9 years [10]. Terminal renal failure is diagnosed in 1.4%–3.2% of the patients [5,19]. The data of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) show that 2.6% of transplantations are performed on D+ HUS patients [20]. In our study, terminal renal failure was diagnosed in 6.2% ($n = 2$) of the children, and both underwent cadaveric renal transplantation.

Historically, the overall acute mortality rate of about 30% has declined dramatically with the introduction of early dialysis for severely affected oligo-anuric patients. The application of modern medical care has decreased the mortality rate to 1%–10% [16,18,21–24]. Our data confirm the findings of other studies that neurological sequelae (massive cerebral hemorrhage, cerebral edema) are the most common causes of death, with less frequent causes being bowel necrosis, heart failure, and arrhythmia [9,18,22,25].

Our study confirms that children with a history of D+ HUS are at a greater risk of developing new symptoms and must be followed for a long time [3,22,26]. The Austrian study provided data indicating that after 5 years, 18% of the patients developed hypertension and proteinuria, while after 1 year, there were no residual symptoms of the disease. It was therefore concluded that HUS patients should be followed for at least 5 years [3]. There is a need for longer-term observational studies because it is known that new symptoms may appear 10 years after recovery, and it is difficult to predict the level of renal function after 3–4 decades. The 32-year long-term study in Argentinian showed that 12 years after the diagnosis 15% of the children developed new kidney-damaging conditions, such as hypertension, proteinuria, microalbuminuria and decreased eGFR [16]. The Spanish study by Lumbreras et al. followed up patients for 28 years and found that 21.6% of them had decreased eGFR, 35% had hypertension and proteinuria, and 8% had terminal renal failure [27]. We found that after ≥10 years, 33.3% of the patients did not develop any clinical changes. These findings are consistent with

other studies showing that 30%–48.4% of patients remain fully recovered after ≥ 10 years [3,6,22,26]. There is no unanimous opinion on the length of time D+ HUS patients should be followed. All authors suggest, however, that patients should be followed for at least 5 years, because most clinical changes occur during this period [3,4]. Because our data show new symptoms appearing even at ≥ 10 years after recovery, we recommend periodic follow-up for 10 years from the onset of the disease, with further follow-ups for patients with chronic illness.

In summary, the acute phase of HUS can be followed by temporary recovery with symptoms of chronic disease developing later. It is therefore appropriate to assess D+ HUS as a chronic disease, as its full prognosis can only be determined after a long follow-up period.

5. Conclusions

In our study, 82.3% of the children diagnosed with typical HUS were younger than 5 years. More than 10 years after the onset of the disease, hypertension was detected more often in those children who were aged < 1 year at the time of the diagnosis, and 6.1% of the children had developed hypertension for the first time. Proteinuria persisted more often in children who had it during the acute phase; however, 6.1% of the patients developed it for the first time after ≥ 10 years. Five years after the onset of the disease, 39.5% of the children had renal failure of various degrees, which progressed in most of them during the follow-up period. Children having hypertension at the onset were more likely to experience a decreased eGFR. Neurological sequelae (massive cerebral hemorrhage, treatment-resistant cerebral edema) and bowel necrosis were the main causes of death. These findings emphasize the necessity of monitoring children for more than 10 years after a typical HUS episode. They should be closely followed up by pediatric nephrologists for renal function and other significant factors such as hypertension and proteinuria.

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