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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.

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 $>20 \times 10^9$ 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 $<150 \times 10^9$ 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 m^2 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