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Long-Term Outcome of Children Previously on Dialysis Therapy for Hemolytic Uremic Syndrome

Odległe losy dzieci leczonych dializami z powodu zespołu hemolityczno-mocznicowego

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Abstract

Background. Hemolytic uremic syndrome (HUS) is the most common cause of acute renal failure of renal origin in small children.
Objectives. The aim of the study was to evaluate renal replacement therapy results and the follow-up of children with diagnosed HUS treated at the Department and Clinic of Pediatrics in Zabrze, Medical University of Silesia, between 1990 and 2006.
Material and Methods. The medical records of 43 children (14 girls, 29 boys) with a mean age 46.3 ± 50 months at the time of dialysis treatment were analyzed. The mean hospitalization time was 49.1 ± 34.9 days. The mean duration of renal replacement therapy was 15.0 ± 19.9 days. The mean time of anuria was 5.5 ± 8.2 days. Peritoneal dialysis was administered in 33 children and hemodialysis in 9 as the main method of treatment. Typical HUS was diagnosed in 16 children and atypical HUS in 19 (including 2 children with chronic glomerulonephritis). HUS was of recurrent origin in 2 children. Four children (9.3%) died at the acute phase of disease and one (2.3%) died during end-stage renal failure one year after the onset of HUS. Clinical status on admission was analyzed (including the history of hypertension and co-morbidities). Systemic hypertension was present in 14 children (32.6%) at the onset of HUS. Initial laboratory test values were also analyzed. The status of 36 children was analyzed at the end of treatment and outpatient observation. The mean time of ambulatory observation was 5.15 ± 4.37 years.
Results. End-stage renal failure was established in 3 children (8.4%). Chronic renal disease of grades 2-4 was found in 6 (16.7%) children, arterial hypertension in 22 (61%) which required medication with mean 2.4 ± 1.3 hypotensive agents, and proteinuria was present in 6 (16.7%) children. In 5 children (13.9%) organ complications of hypertension, such as left ventricle thickening, were detected. Negative correlation between the duration of renal replacement and mean glomerular filtration rate (GFR) after 5 years of observation was observed.
Conclusions. HUS should be the main disease entity considered in the differential diagnosis of small children with acute renal failure and anemia in the course of diarrhea infection. Children with severe HUS should be quickly referred for renal replacement treatment. In view of the impaired renal function and target organ complications after HUS, constant care by a nephrologist is necessary (**Adv Clin Exp Med 2008, 17, 147–153**).

Key words: hemolytic uremic syndrome, children, renal replacement therapy, long-term outcome.

Streszczenie

Wprowadzenie. Zespół hemolityczno-mocznicowy (z.h.m.) jest najczęstszą przyczyną pochodzenia nerkowego ostrej niewydolności nerek u małych dzieci.
Cel pracy. Ocena wyników leczenia nerkozastępczego i dalszych losów dzieci z z.h.m. hospitalizowanych w Klinikach Pediatrii ŚUM w Zabrzu w latach 1990–2006.
Materiał i metody. Analizowano dokumentację medyczną 43 dzieci (14 dziewczynek, 29 chłopców) w wieku średnio 46,3 ± 50 miesięcy w chwili rozpoczęcia dializoterapii. Średni pobyt w szpitalu trwał 49,1 ± 34,9 dni. Dzieci były leczone nerkozastępczo średnio 15,0 ± 19,9 dni. Średni czas trwania bezmoczu wynosił 5,5 ± 8,2 dnia. Jako główną metodę leczenia u 33 dzieci stosowano dializę otrzewnową, hemodializy u 9 dzieci. U 16 dzieci stwierdzano typowy z.h.m., u 19 – atypowy (w tym u 2 w przebiegu kłębuszkowego zapalenia nerek). U 2 dzieci z.h.m. charakteryzował się nawrotami. Czworo dzieci (9,3%) zmarło w ostrym okresie choroby, jedno (2,3%) –

w fazie schyłkowej niewydolności nerek po roku od wystąpienia z.h.m. W pracy zanalizowano stan kliniczny dzieci podczas przyjęcia do Kliniki z uwzględnieniem występowania nadciśnienia tętniczego i chorób dodatkowych. Nadciśnienie tętnicze podczas przyjęcia stwierdzono u 14 dzieci (32,6%). Zanalizowano wstępne badania laboratoryjne. Oceniono stan 36 dzieci w końcu leczenia i obserwacji w poradni przyklinicznej. Średni czas obserwacji w poradni przyklinicznej wynosił 5,15 ± 4,37 roku.

Wyniki. Schyłkowa niewydolność nerek wystąpiła u 3 dzieci (8,4%). U 6 (16,7%) dzieci stwierdzono przewlekłą chorobę nerek w stadium 2–4, u 22 (61%) dzieci – nadciśnienie tętnicze, które wymagało zastosowania średnio 2,4 ± 1,3 leków hipotensyjnych, u 6 (16,7%) dzieci – białkomocz. U 5 (13,9%) dzieci występowały narządowe powikłania nadciśnienia tętniczego pod postacią pogrubienia mięśniówki lewej komory serca. Wykazano ujemny związek długości leczenia nerkozastępczego ze średnią wartością GFR po 5 latach obserwacji.

Wnioski. Małe dzieci z objawami ostrej niewydolności nerek i niedokrwistością poprzedzonymi biegunką powinny być diagnozowane w kierunku z.h.m. Dzieci z rozpoznanym ciężkim z.h.m. należy jak najszybciej kierować do leczenia nerkozastępczego. Ze względu na zaburzenie czynności nerek oraz powikłania narządowe po przebytym z.h.m. jest konieczna stała opieka nefrologa (**Adv Clin Exp Med 2008, 17, 147–153**).

Słowa kluczowe: zespół hemolityczno-mocznicowy, dzieci, leczenie nerkozastępcze, odległe rokowanie.

Hemolytic uremic syndrome (HUS) is defined as thrombotic microangiopathy with thrombocytopenia (from wasting), hemolytic anemia and, renal impairment due to platelet thrombi in the microcirculation of the kidney. Gasser et al. reported in 1955 for the first time the cases of five children with hemolytic anemia, thrombocytopenia, and acute renal failure and named the disease HUS [1]. Most authorities consider endothelial injury as the principal factor that sustains the microangiopathic process [2–8]. The frequency of HUS in children under five years old is 2–7/100,000. In children under three years of age, hemolytic uremic syndrome is the most frequent cause of acute renal failure [7].

HUS is currently subdivided into the typical diarrhea associated (D^+) form, which comprises up to 90% of cases, and an atypical form without prodromal diarrhea (D^-) and secondary disease. D^+ HUS is seasonal and has its peak incidence in warm summer. Relapses are rare in D^+ HUS [7–9]. Epidemic incidence of HUS is possible in children [10]. In adults, HUS exists as Moschcowitz's syndrome (thrombocytopenic purpura, fever, and neurological involvement) [6]. The symptoms in a child with diarrhea which should alert the attending physician to a possible diagnosis of HUS are irritability, which appears immediately, prostrating, drowsiness, pallor with a discrete yellowish tint of skin, and conjunctivas, rarely petechiae, oliguria, and the appearance of edema during rehydration. Small children with symptoms of acute renal failure with anemia should be diagnosed to detect the features of HUS early.

A common clinical manifestation of HUS in a child is hemolytic anemia, with a hemoglobin level below 8 g/dl, thrombocytopenia, occasionally connected with hemorrhagic diathesis, i.e. bruises, petechiae, spontaneous ecchymoses, nose bleeding, bleeding to the vitreous body, choroidea, or retina, or bleeding from the genitourinary or digestive system [7]. Characteristic for the disease is arterial hypertension and renal impairment, seen as erytrocyturia, hematuria, proteinuria, and features of acute renal failure [11]. About 50% of children have oliguria. Pancreatic involvement occurs in 20% of cases, most often of subclinical course. The same percentage of cases involves neurological involvement, with symptoms of paresis, aphasia, headache, disorders of consciousness, sight disorders, seizures, and coma [12, 13]. The next complication is hemorrhagic enterocolitis, with the incidence of 10–20% of cases, with anal prolaps, black stools, and digestive system obstructive symptoms [14]. Liver function disorders are present in 40% of cases and combine hepatomegaly and increased levels of transaminases. In the clinical picture of HUS, myocarditis and lung disorders are also found [6–8].

The diagnosis of HUS is made after detecting anemia, a rise in reticulocyte number, schistocyte presence (2–10%) in the peripheral blood smear, and detection of erythrocyte fragments. Increased LDH activity, increased direct bilirubin level, free hemoglobin in plasma, negative Coomb's test, frequently leukocytosis, thrombocytopenia 40–60 $\times$ 10^9/l, with "large" platelets, disproportionate increase in uric acid in the serum than blood urea nitrogen and creatinine, hyponatremia, hypocalcemia, and metabolic acidosis are present [2, 5, 15]. The constant symptom is also arterial hypertension [16].

In the treatment of children with acute renal failure symptoms with oliguria and/or anuria, dialysis is the method of choice. The indications for dialysis have been established over many years of experience in different parts of the world. Early institution of this treatment allows for lowering the mortality rate. The best option is peritoneal dialysis. Chronic hemodiafiltration is an effective and safe alternative of acute renal replacement therapy in the management of renal failure in pediatric cases with aggravated HUS with abdominal com-

plications [17]. An early start of symptomatic treatment is of particular importance to achieve a mortality rate below 5%.

This study's aim was to evaluate the results of renal replacement treatment and the follow-up of children with hemolytic uremic syndrome hospitalized at the Department and Clinics of Pediatrics in Zabrze of Silesian Medical University in Katowice from 1990 to 2006.

Material and Results

The medical records of 43 children, 14 girls (32.6%) and 29 boys (67.4%), with a mean age of 46.3 ± 50.0 months (range: 5.4 months to 17 years) at the time of the start of dialysis treatment, were reviewed. The mean duration of hospitalization was 49.1 ± 34.9 days (range: 9–152 days). The mean duration of renal replacement treatment was 15.0 ± 19.9 days (range: 7–126 days). The mean duration of anuria was 5.5 ± 8.2 days (range: 0–33 days).

Peritoneal dialysis was applied as the principal method of renal replacement therapy in 33 children (76.7%) and hemodialysis in 9 children (23.3%). Typical HUS was diagnosed in 16 children (37.2%) and atypical HUS in 19 (44.2%) (including two children with glomerulonephritis). In 8 children there were data lacking in the medical records about prodromal signs of HUS. In 2 children (4.65%) the course of HUS was recurrent. Four children (9.3%) died in the acute phase of the disease and one (2.3%) during end-stage renal insufficiency one year after the onset of HUS.

The blood group distribution was: 15 children (34.9%) with A Rh (+), 6 (14%) with A Rh (–), 7 (16.3%) with B Rh (+), 3 (7%) with B Rh (–), 8 (18.6%) with 0 Rh (+), 1 (2.2%) with 0 Rh (–), and 3 (7%) with AB Rh (+). Anthropometrical parameters and laboratory test results of the examined children are shown in Table 1.

The clinical status at admission to hospital was also analyzed. The presence of arterial hypertension and co-morbidities was particularly of interest. Four children showed the symptoms of cerebral palsy. Arterial hypertension was detected at admission in 14 children (32.6%). In the acute phase of disease a mean volume of 958.2 ± 1038.0 ml plasma and 1140.7 ± 1817.4 ml red packed cells was transfused.

Clinical status and laboratory tests results were evaluated in 36 children at discharge from the hospital after the acute phase and at the end of outpatient observation. The mean time of ambulatory observation was 5.15 ± 4.37 years (range: 5 months to 16.8 years).

Table 1. Anthropometrical parameters and laboratory tests results in examined children

Tabela 1. Wskaźniki antropometryczne i wyniki laboratoryjne u badanych dzieci

Parameter (Wskaźnik)	Admission (Początek leczenia) n = 43	Follow-up (Koniec obserwacji) n = 36
Height (Wzrost) cm	100.5 ± 33.3	130.0 ± 33.5
Body weight (Masa ciała) kg	17.3 ± 13.9	33.8 ± 20.8
BMI kg/m^2	17.1 ± 3.27	17.85 ± 3.24
Hemoglobin (Hemoglobina) g/dl	7.64 ± 1.85	13.3 ± 1.4
Erythrocytes (Erytrocyty) T/l	2.74 ± 0.64	4.61 ± 0.51
Hematocrit (Hematokryt) %	22.41 ± 6.02	37.7 ± 4.0
Leukocytosis (Leukocyty) G/l	12.54 ± 6.88	7.37 ± 2.62
Platelets (Płytki krwi) G/l	67.89 ± 57.93	272.85 ± 78.42
Creatinine (Kreatynina) umol/l	226.56 ± 133.13	108.76 ± 224.59
Uric acid (Kwas moczowy) umol/l	534.94 ± 215.63	242.61 ± 102.27
Urea nitrogen (Azot mocznikowy) mmol/l	20.99 ± 9.02	5.83 ± 4.97
Total proteins (Białko całkowite) g/l	53.49 ± 9.27	72.35 ± 9.83
Bilirubin (Bilirubina) umol/l	41.30 ± 38.11	/
GPT IU/l	63.0 ± 53.1	/
GOT IU/l	104.65 ± 63.12	/
Na^+ mmol/l	132.27 ± 6.23	/
K^+ mmol/l	4.46 ± 0.90	/
Ca^{+2} mmol/l	1.12 ± 0.1	/
Total Ca (Wapń całkowity) mmol/l	2.18 ± 0.34	/
P mmol/l	1.88 ± 0.45	/
Proteinuria g/l	7.52 ± 9.11	1.7 ± 3.2

Table 2. Correlation coefficients between examined parameters and the value of GFR after 5 years of observation

Tabela 2. Współczynniki korelacji między badanymi wskaźnikami a GFR po 5 latach obserwacji

GFR	Examined parameter (Badany oparametr)						
	age at onset	body weight	height	BMI	SBP	DBP	MAP
Correlation coefficients (Współczynniki korelacji)	–0.2310	–0.2173	–0.1652	0.0961	–0.3141	–0.3759	–0.3574
	hemoglobin	erythrocyte number	hematocrit	creatinine	urea nitrogen	Na	K
Correlation coefficients (Współczynniki korelacji)	0.2150	0.2015	0.1861	0.0399	0.0704	0.1128	–0.0746
	bilirubin	GPT	GOT	P	uric acid	total proteins	Ca^{2+}
Correlation coefficients (Współczynniki korelacji)	–0.1023	–0.1909	0.1777	–0.0395	–0.2117	0.1535	0.3367

	blood transfusions	plasma transfusions	dialysis duration	anuria duration	proteinuria
Correlation coefficients (Współczynniki korelacji)	–0.3383	–0.2505	**–0.5370**	0.0155	0.1535

End-stage renal insufficiency appeared in 3 children (8.4%). Six (16.7%) revealed chronic renal disease stages 2–4 and arterial hypertension was observed in 22 (61%). In these children, the mean number of anti-hypertensive drugs was 2.4 ± ± 1.3. In 6 (16.7%) children, constant proteinuria was present at the end of observation. In 5 children (13.9%) late organ consequences of arterial hypertension, such as wall hypertrophy of the left ventricle of the heart, were present. In the analysis of correlations of baseline laboratory test results, anuria duration, renal replacement therapy duration, and blood pressure values with mean glomerular filtration rate (GFR) at the end of observation, no significant relationship was found except for the negative correlation between GFR and renal replacement therapy duration. The correlation coefficients are shown in Table 2.

Discussion

Agents that may be found among the causes of HUS include bacterial pathogens, such as *Escherichia coli*, *Shigella dysenteriae*, *Salmonella typhi*, *Streptococcus pyogenes*, neuraminidase-producing microorganisms (e.g. *Streptococcus pneumoniae*), and *Campylobacter* species. The main source of infection is contaminated food and water, rarely occupational exposure. HUS is most often observed after ingestion of unpasteurized milk, cheese, undercooked beef, after the use of water from wells or lakes, and after meals with contaminated fruits, vegetables, or juice. Toxins can also bind secondarily with polymorphonuclear leukocytes of the peripheral blood. The expression of glycolipid receptors for verotoxin localized in the kidneys (Gb3 protein: globotriaosylceramide) has been recently detected. In the pathogenesis of D^+ HUS, toxins play the key role, e.g. *E. coli* verotoxin, especially 0157: H7 (VTEC) 0111, 0103: H2, 026:H11 serotypes, and cytotoxins of *Shigella dysenteriae* 1 type (STEC, Stx) and *Salmonella typhi*, which cause renal endothelial damage and platelet aggregation [2, 3, 5, 9].

Viral infection (e.g. HIV, CMV, Coxsackie virus, echovirus, influenza, chickenpox, EBV) could be a leading cause of HUS as well. This syndrome is also observed after the ingestion of oral contraceptive pills, mitomycin C, cytosine arabinoside, the combination of bleomycine and cisplatin, cyclosporine A, tacrolimus, OKT3, quinine, ticlopidine, clopidogrel, and interferon β [18]. Anti-diarrheal drugs are also responsible for the development of HUS as they prevent rapid elimination of pathogens from the digestive system. HUS can be perceived as a mask of various diseases e.g. EPH gestosis, systemic lupus erythe-

matosus, sclerodermia, tumors, malignant hypertension, or methylmalonic acidosis also occur after organ transplantation [9, 19]. For D^- HUS, antibodies against endothelial cells, immunological complexes, abnormal multimers of von Willebrand's factor, severe deficiency of von Willebrand factor-cleaving protease (ADAMTS-13) activity, and factor H deficiency have been localized [20–22]. Other factors that play roles in the development of HUS symptoms are increased adhesion and aggregation of platelets (glycoprotein IIb/IIIa surface receptor mediated), decreased platelet aggregation-inhibitor concentrations (e.g. IgG), kidney hypoperfusion with subsequent arterial hypertension, increased concentration of inhibitor of plasminogen tissue activator (PAI-1), decreased PGI2, nitric oxide, or thrombomoduline concentrations, presence of circulating lupus anticoagulant during pregnancy and delivery, and the release of TNF and IL-1 *in situ* in the kidney [2, 6, 15, 23, 24].

Due to the various pathogens and causes of HUS, the treatment of the acute phase of disease presents a great challenge to a medical team. There is no straightforward scheme for HUS management. In some cases the application of dialytic therapy, plasma infusions, or plasma exchange could be curative [25, 26]. Children with severe HUS should be referred for the renal replacement treatment early. Ito et al. described the successful application of intravenous gamma globulin for thrombotic microangiopathy of unknown etiology for a dialyzed child with HUS. This could be an option in patients refractory to conventional treatment [27]. Caprioli et al. have shown in genetic studies that mutations in complement regulatory proteins predispose to non-Shiga toxin-associated HUS. They performed genetic analysis on membrane cofactor protein (MCP), complement factor H (CFH), and factor I in 156 patients with HUS. Kidney transplantation outcome was favorable in patients with MCP mutations, whereas the outcome was poor in patients with CFH and IF mutations due to disease recurrence [28]. In the selected cases with genetically proven mutations, liver-kidney transplantation has been implemented as the method of treatment. [29, 30].

With improvement in the early outcome of HUS, interest is currently shifted to treating its severe long-term consequences [5, 11, 16, 22]. Żurowska et al. followed 105 patients for a mean of 1 year. The survival rate in this group of patients improved dramatically over the years, to 97% in the 1990s. The longer the follow-up, the greater the percentage of patients in this group who showed severe outcome. At the last follow-up only 32% of the children showed full recovery. Thirty-three percent were on renal replacement therapy or had impaired renal function. The duration of anuria was a marker of poor late prognosis. [31]. The survival rate in children with HUS observed by the present authors was 92.7%. It was found that 25.1% of the children reached chronic renal disease stages 2–5 and 61% had the symptoms of arterial hypertension. The present authors also confirmed deterioration of clinical status in children with a longer time of observation, but the duration of anuria has not been the parameter of prognostic importance. Dobiliene et al. reported arterial hypertension in 20%, proteinuria in 20%, and chronic renal insufficiency in 60% of children. They studied a group of 20 children, of whom 15 had a severe course of disease at the acute phase, with the need for renal replacement therapy [32]. In the present authors' group of children with HUS, hypertension had more severe consequences, with organ involvement in 13.9% of children. Also, more than 50% of adult cases revealed hypertension [6].

Persistent proteinuria is regarded as a marker of renal damage and as a prognostic factor in the progression of renal disease. In the present authors' group, 16.7% of children followed up after HUS had proteinuria; unfortunately, microalbuminuria was not measured. Data from the literature suggest the value of this parameter together with proteinuria in determining the outcome of HUS. Lou-Meda et al. demonstrated the prognostic significance of microalbuminuria in postdiarrheal HUS with 6–18 months following the episode of HUS [33]. Cobeñas et al. examined the records of 130 patients with HUS who had not undergone dialysis during the acute stage of disease. After a mean follow-up period of 12 years, 15% of these patients had developed proteinuria, high blood pressure, or chronic renal failure and 21% had developed microalbuminuria. Peak serum creatinine during the acute stage was useful as a prognostic indicator. Patients whose renal function required more time to normalize did not have orse outcome [34]. In the present authors' patients with HUS which required renal replacement therapy, its duration was the negative factor in the progression of renal disease. ABO antigens and the number of transfusions were not associated with the outcome of HUS.

The authors conclude that young children with symptoms of acute renal failure with anemia should be diagnosed to detect the features of HUS early. Children with severe HUS should be quickly referred for renal replacement treatment. In view of the renal function impairment and target organ complication after HUS, constant care by a nephrologist is necessary.

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