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DIALYSIS TREATMENT IN CHILDREN WITH AMYLOIDOSIS DUE TO JUVENILE RHEUMATOID ARTHRITIS*

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Rapid deterioration of renal function in amyloidotic children may be due to progression of amyloidosis or exacerbation of chronic renal failure (CRF). Continuous ambulatory peritoneal dialysis (CAPD) is superior to hemodialysis (HD) both in end-stage renal disease and in exacerbations of CRF in amyloidosis.

A better supply of protein and easier control of hypertension are possible on CAPD, while HD is associated with the risk of hypovolemia episodes, cardiovascular disturbances and bleeding connected with heparinization. *Key words: renal amyloidosis, continuous ambulatory peritoneal dialysis, chronic renal failure.*

Systemic amyloidosis is an important cause of morbidity and mortality in juvenile rheumatoid arthritis (JRA). Renal involvement manifests itself as nephrotic syndrome (NS) with a variable degree of renal damage and may progress to end-stage renal disease (ESRD)[1-6]. The current thinking about renal replacement therapy in children with amyloidosis is mixed. The purpose of this study was to assess the progress of disease and the results of dialysis treatment in children with JRA and amyloidosis.

Material and Methods

Eight children with JRA and amyloidosis were referred from the Institute of Rheumatology between 1980 and 1991 because of deterioration of renal function. Their disease met the American Rheumatic Association's criteria for diagnosis of systemic JRA[7]. The patients' ages at onset of JRA ranged from 1.3 to 8.3 years.

Amyloidosis was suspected when proteinuria or frequent exacerbations of JRA appeared. NS was defined as proteinuria greater than 50 mg/kg/day and a serum albumin level less than 2.5 g/dl. Renal insufficiency was diagnosed when the serum creatinine level exceeded the upper normal laboratory limit of 1.0 mg/dl.

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Amyloidosis was confirmed by renal and/or gingival biopsy in all patients. The biopsy specimens were stained for amyloid with Congo red[8] and Sirius red[9].

Prior treatment of JRA consisted of non-steroidal anti-inflammatory drugs (NSAID) in all patients. The next medication for disease control was corticosteroids at a daily dose of 0.5-1.0 mg/kg depending on JRA activity. During exacerbations of JRA, children received methylprednisolone intravenously.

Chlorambucil at an initial daily dose of 0.1 mg/kg was given to patients (Cases 1, 3, 4, 5, 7, 8, Table I) when proteinuria appeared. For active, severe polyarthritis and the presence of active extraarticular features (fever, hepatosplenomegaly), Cases 1 and 3 received cyclophosphamide, and Case 3 colchicin, but without good effects.

Table I: Characteristics of Patients with Amyloidosis

	Age Diagnosis (years)						
Patient	JRA	Proteinuria	NS	Renal Failure	Creatinine at Renal Insufficiency Diagnosis (mg/dl)	Age at Biopsy: Renal* Gingival**	Age at Start of Dialysis: (years)
1	4 6/12	–	8 3/12	10 7/12	1.3	8 5/12*	11
2	3 9/12	–	7 5/12	7 5/12	4.6	7 6/12*	7 5/12
3	8 4/12	9 10/12	11 5/12	11 5/12	1.2	10 5/12*	11 7/12
4	8	9 10/12	11 10/12	12 5/12	2.5	9 10/12**	14 11/12
5	3 3/12	–	5 10/12	9 4/12	9.2	6*	9 10/12
6	3 10/12	5 7/12	6 4/12	8 5/12	1.8	8 7/12*	8 6/12
7	1 4/12	10 7/12	12 9/12	12 9/12	1.51	11 1/12*	15 2/12
8	2	–	7	7 7/12	1.1	4**	–
						9 3/12*	

The course of the disease in all patients is shown in Table I. All patients with chronic renal failure (CRF) during the predialysis period and on hemodialysis (HD) were given a diet recommended for height age. A high-protein diet (protein > 2g/kg/day) was given to patients on continuous ambulatory peritoneal dialysis (CAPD).

All children underwent dialysis (HD and/or CAPD). The indications to start dialysis treatment in cases 1, 2, 3, 4 and 8, despite relatively low creatinine levels, were rapid increase of BUN and creatinine level, acidosis, decreased diuresis, in Cases 2, 3, 4, 7 and 8, and ESRD in Cases 5 and 6 severe overhydration and hypertension (Table II).

HD was performed three times weekly for an average of nine hours per week. CAPD was started with four to five exchanges per day. If renal function improved, the initial regimen was reduced to three exchanges.

Table II: Data of Dialyzed Patients

Patients	Creatinine Before Exacerbation mg %	Creatinine mg/dl	BUN mg/dl	Albumin g/dl	Proteinuria mg/kg/d	Diuresis ml/kg/d	Acidosis	BP mmHg	Months on Dialysis HD	Months on Dialysis CAPD	Outcome
1	0.57	5.8	94	2.5	70	37.5	+	↑	3	12	ESRD after exacerbations of JRA BP, transplanted
2	0.96	6.0	120	2.0	110	12.5	+	–	0.5	3	Improvement of Renal Function, BP°
3	0.8	6.3	95	1.8	188	19.0	+	↑	1	3	
4	1.9	5.0	117	1.5	480	11.5	+	↑	0.5	–	Cardiovascular disturbances, BP°, died
5	6.0	13.0	64	2.6	250	20.0	–	↑	–	17	ESRD, BP°°, Good rehabilitation
6	1.8	16.0	84	1.6	250	9.0	–	↑	12	–	ESRD, BP°°, Cardiovascular disturbances, died
7	1.51	6.63	114	4.8	70	20 → 0	–	↑	5/12	10	ESRD, BP°°, Good rehabilitation
8	1.67	2.55	76	3.4	128	50	+	↑	–	3	ESRD, BP°°, Good rehabilitation

BP° : normal blood pressure.

BP°° : good control of blood pressure.

The serum creatinine level and BUN were checked after a three-day interval without dialysis. Renal ultrasound (US) was performed with a Siemens SL Unit with 3.5 and 5 MHz transducers operating in real time. The size of the kidney was evaluated in relation to the child's height[10].

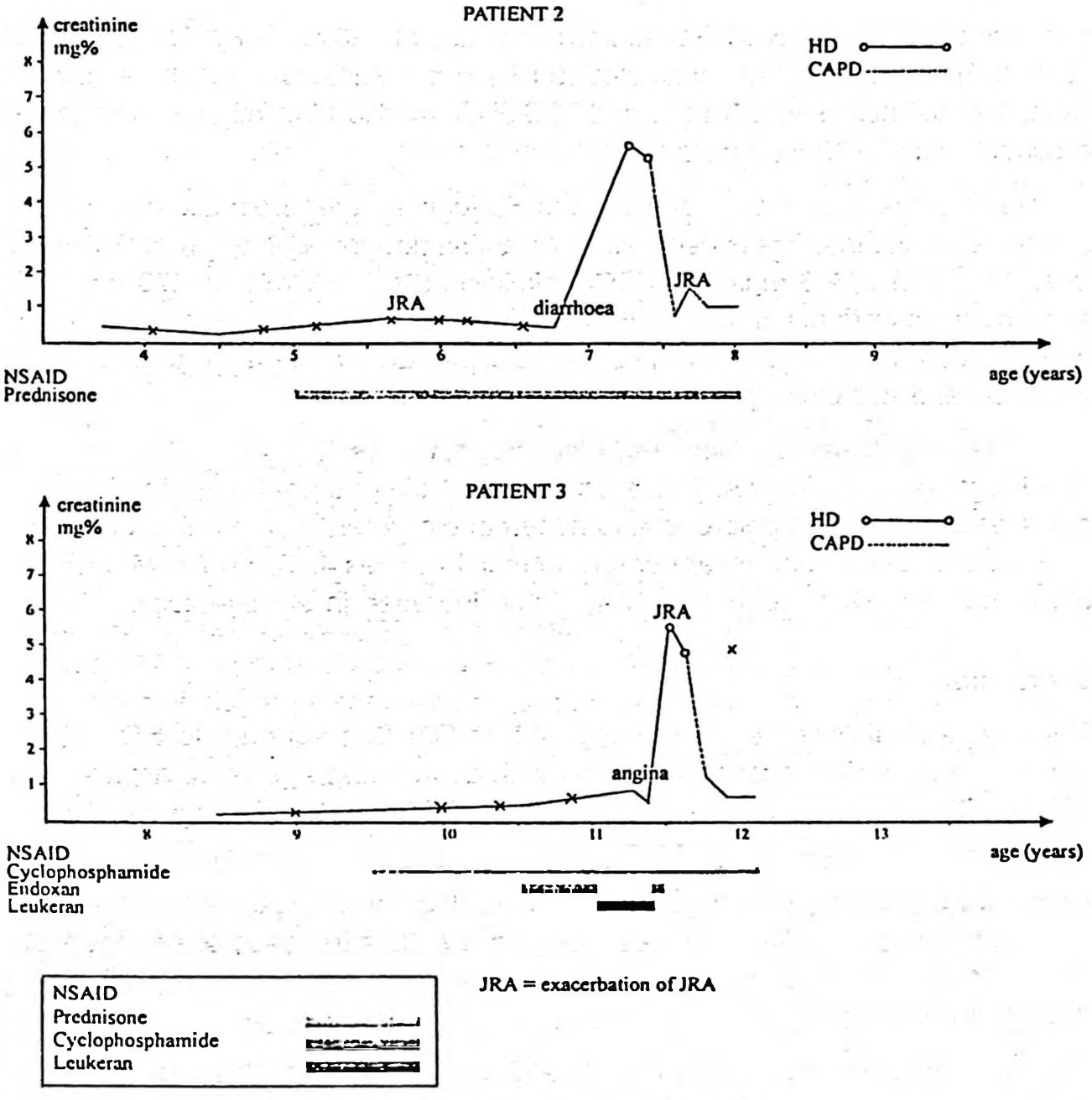
Results

The data of the dialyzed patients are shown in Table II. Progressive weakness, weight loss, diminishing diuresis, and bleeding from the gastrointestinal and respiratory tracts were observed in Case 1 over three months on HD. Considerable improvement of his general condition, regression of articular features and good quality of life were achieved despite ESRD when the child was transferred to CAPD. After a year on CAPD the child was successfully transplanted.

Cases 2 and 3, after 15 days and one month, respectively, on HD with episodes of hypotension and no improvement in renal function, were transferred to CAPD. Over a period of three to four months their renal functions gradually improved (Table III, Figs 1-2).

Table III: Laboratory Data of Amyloidotic Children with Exacerbation of CRF Treated with CAPD

Patient	Time on Dialysis (months)		Creatinine mg/dl	Diuresis ml/day	Proteinuria mg/kg/day	Effects
	HD	0.5	6.0→5.0	200	110	Oliguria
		1	5.0→1.8	1000	43	Renal function improvement
	C					
2	A					
	P	2	1.8→1.5	1400	46	
	D					
		3	1.5→1.3	1100	49	
	2 months after stopping dialysis		1.5	2000	75	
	HD	1	6.3→5.07	950	188	Oliguria Overhydration
		1	5.07→1.6	1000	36	Renal function improvement
	C					
	A					
3	P	2	1.6→1.3	1300	58	
	D					
		3	1.3→1.1	2000	63	
	2 months after stopping dialysis		1.1	1700	35	



Figs. 1-2: The course of disease and treatment regimen in two amyloidotic children.

After two weeks on HD, Case 4 died with signs of cardiovascular failure and myocardial ischemia.

After seventeen months on CAPD, Case 5 was in good condition, while case 6 on HD had frequent episodes of hypotension, hypertension and poor rehabilitation, and died after a year with signs of cardiovascular disturbance and gastrointestinal bleeding.

In Case 7, CAPD was started when the patient's serum creatinine level was 6.63 mg/dl and evaluated creatinine clearance (ECC) was 10.45 ml/min/1.73 m^2 with diminishing diuresis and coexisting hypertension requiring four antihypertensive drugs,

and after three months on CAPD, diuresis increased to 30-40 ml/kg/day, ECC was 12.37 ml/min/1.73 m^2. CAPD was stopped for one month, after which her serum creatinine level increased to 6 mg/dl and ECC diminished to 11 ml/min/1.73 m^2 despite a correct diet. CAPD was restarted.

After ten months Case 7 was transferred to HD for five weeks because of recurrent peritonitis. During that time hypertension and anuria developed, the serum creatinine level increased to 9.3 mg/dl and ECC diminished to 7.48 ml/min/1.73 m^2. JRA exacerbations were not observed. Prednisone was given at a daily dose of 5 mg, and she was transferred to CAPD again. Despite ESRD she is in good general condition and her blood pressure is well controlled.

US of the patients revealed various kidney sizes. Cases 1, 7 and 8 had normal-sized, hyperechoic kidneys. At the beginning of dialysis treatment, the kidneys of Cases 2 and 3 were enlarged and hyperechoic. After three months on CAPD their sizes and echogenicity appeared normal. In Cases 4, 5, and 6 with ESRD, the kidney size was reduced with a diffuse increase in echogenicity.

Discussion

The effects of dialysis treatment suggest that CAPD is superior to HD both in the treatment of CRF exacerbations as well as in end-stage renal amyloidosis (ESRA). Differentiation between exacerbation of CRF and ESRA may be difficult in children with rapid deterioration of renal function.

Repeated US is useful as it reveals transient kidney enlargement during CRF exacerbations and reduced kidney size with a diffuse increase of echogenicity in patients with ESRD, although the kidney size in renal amyloidosis is traditionally thought to be enlarged[11].

The early commencement of CAPD treatment in CRF exacerbations seems to be beneficial. HD treatment is definitely not tolerated as well by young amyloidotic patients than by children of the same age with other types of nephropathy.

CAPD makes it possible to avoid episodes of hypotension and bleeding during HD and improves control of hypertension which is particularly important when albumin infusions are necessary in overhydrated children with depleted intravascular volumes. Hypovolemia plays an important role not only in the development of CRF exacerbations but also in late prognosis. The nephrotic range of proteinuria despite advanced CRF was a characteristic feature in our patients, perhaps due to decreased renal tubular transport of protein in renal amyloidosis. CAPD made it possible to introduce a high-protein diet leading to improved protein balance. In some authors' opinions, in hypoalbuminemic adult patients with ESRA and heavy proteinuria, CAPD can worsen the condition[5].

In our patients on CAPD, increases in serum albumin levels were observed, despite heavy proteinuria. In three children treated initially with HD, a significant improvement was seen when they were transferred to CADP. In two of them in whom retrospective analysis of the course of the disease indicated exacerbation of CRF, a significant improvement of renal function was noticed after three months on CAPD. In another child who also had exacerbation of renal failure and was treated with HD for several months, deterioration of renal function led to ESRD. When the patient was transferred to CAPD, renal function remained unchanged but the degree of rehabilitation improved noticeably. All of the patients with ESRD on CADP are in good general condition, with serum creatinine levels ranging from 6.0 to 7.8 mg/dl.

In light of the observed improvement in renal function in the two above-mentioned children with CRF exacerbations treated with CAPD, it may be speculated that earlier introduction of CAPD in the latter child may also have been beneficial.

In adults with ESRA several advantages of CAPD over HD were noted: a similar incidence of peritonitis as in non-amyloidotic patients on CAPD, satisfactory quality of life, freedom of the circulatory stress of HD, better preservation of hemoglobin level, no need for heparinization and vascular access[2, 12, 13]. Good control of uremia suggests adequate dialysis and ultrafiltration across the peritoneum of amyloidotic children.

Besides the advantages of CAPD mentioned above, one cannot rule out the possibility that peritoneal dialysis removes some serum precursors of amyloid A protein (AA), which is the major component of different types of human secondary amyloidosis. This hypothesis requires further study.

The precursor of AA is serum amyloid A (SAA) of molecular weight of 84,000 to 200,000 daltons. SAA is probably a polymer of low-molecular-weight subunits called SAAL, bound to albumin or lipoproteins[13-15]. We hypothesize that elimination across the peritoneum of some medium-sized or low-molecular precursors of AA may limit the progression of amyloid deposition.

At the present time little experience has been reported with CAPD in amyloidotic children with ESRD and with CRF exacerbations. This treatment modality is very useful in children with ESRD, and its role in exacerbations of CRF has yet to be evaluated.

The hypothesis that CADP might improve the outcome of the disease is difficult to confirm because many other factors could also contribute to improved outcome with periodic exacerbations.

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