NEOPTERIN, MCP-1 AND MCSF AS NEW MARKERS OF TUBULAR DAMAGE IN CHILDREN WITH CHRONIC KIDNEY DISEASE ON CONSERVATIVE TREATMENT

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INTRODUCTION:

Chronic kidney disease (CKD) is characterized by enhanced migration of immunocompetent cells to the sites of inflammation and subsequent renal fibrosis. The latter is an essential element of progressive and irreversible tubular damage. Various chemotactic agents influence the above mentioned CKD-related complications.

Monocyte chemoattractant protein (MCP)-1, macrophage colony stimulating factor (MCSF) and **macrophage migration inhibitory factor (MIF)** control early stages of cell migratory activity, such as movement of monocytes to the sites of inflammation and their transition into macrophages. Thus, the activity of MCP-1, MCSF and MIF may be treated as a substitute of the inflammation process intensity, monocyte and macrophage activity, as well as cell damage in the course of chemotactic migration and transition. The elevated serum concentrations of MCP-1 and MIF have been found in adults on hemodialysis, whereas increased MCP-1 urine levels characterized children with hydronephrosis.

Neopterin was the only exception in this group, since its production is not a cause, but a consequence of enhanced cell migration and ongoing inflammation. In detail, both monocytes and macrophages excrete neopterin upon stimulation. Therefore, this molecule may be a biochemical marker of cell immunity. The increased serum concentrations of neopterin were observed in adults with advanced stages of CKD. The elevated excretion of neopterin with urine was noticed in adults with mesangioproliferative glomerulonephritis.

The above mentioned parameters have never been analyzed as markers of inflammation or macrophage activity in children with CKD.

Analysis of the **fractional excretion (FE)** of various parameters with urine, as a substitute of tubular dysfunction, has not been used in the CKD patients except for the assessment of the phosphate metabolism so far. Neither MCP-1, MCSF, MIF or neopterin have been tested, in the light of fractional excretion, as potential markers of tubular damage in the course of chronic kidney disease.

AIM OF STUDY:

1) analysis of factors engaged in monocyte migration and their transition to macrophages by assessing the concentrations of MCP-1, MCSF, MIF and neopterin in the serum and urine of children with CKD stages 1 to 5 and of controls
2) assessment of the fractional excretion (FE) of MCP-1, MCSF, MIF and neopterin in children with CKD stages 1 to 5 and in the control group
3) analysis of MCP-1, MCSF, MIF and neopterin applicability as markers of the CKD-related phenomena, like monocyte – macrophage interplay, inflammation and tubular damage.

MATERIAL:

Eighty four patients enrolled in this study were divided into 3 groups. Basic clinical data are shown in **table 1**.

METHODS:

Blood samples were drawn from peripheral veins after an overnight fast. Samples were clotted for 30 minutes, centrifuged at room temperature for 10 minutes, and then serum was stored at -20degC until assayed. Urine was collected aseptically from the first morning sample, centrifuged at room temperature for 10 minutes and then stored at -20degC until assayed.

The serum and urine concentrations of MCP-1, MCSF, MIF and neopterin were evaluated by commercially available ELISA kits (R&D Systems). Measurements were performed according to the manufacturer's instructions, results were calculated by reference to standard curves.

The fractional parameter excretion (FE) was calculated according to the formula:

$$FE = \frac{[\text{urine parameter concentration}] \times [\text{serum creatinine concentration}]}{[\text{serum parameter concentration}] \times [\text{urine creatinine concentration}]} \times 100\%$$

RESULTS:

Serum and urine concentrations of MCP-1, MCSF, MIF and neopterin

The serum and urine concentrations of all examined parameters were significantly enhanced, irrespective of the CKD stage, vs. controls (**tables 2-3**). Serum MCSF and MIF levels rose gradually with the CKD progression, whereas serum MCP-1 and neopterin concentrations in advanced stages of CKD were significantly lower than in mild CKD, although still above the values seen in the control group (**table 2**).

Urine MCP-1 and MIF levels were significantly increased in CKD stages 1-2 vs. controls, but then remained stable despite progression of CKD to stages 3-5 (**table 3**). Urine MCSF concentrations decreased in advanced vs. mild CKD. Urine neopterin levels were the only ones increasing gradually with the CKD progression.

Interestingly, the values of MCSF and neopterin in urine were always higher than the relevant ones in serum, irrespective of the analyzed group.

Fractional excretion of MCP-1, MCSF, MIF and neopterin

The fractional excretion (FE) of MCP-1 and MIF did not exceed 1% in healthy controls, whereas it reached up to 5% in the case of MCSF and neopterin (**table 4**). Only MCP-1 and MCSF FE values were significantly elevated in children with CKD stages 1-2 vs. controls, whereas all FE values were higher in patients with CKD stages 3-5 vs. those with CKD stages 1-2 (**table 4**). However, they remained below 1% for MCP-1 in children with CKD stages 1-2 and for MIF in all children with CKD. The fractional excretion of MCSF and neopterin was far beyond 1% in all CKD patients.

Table 1. Basic characteristics of the patients

Parameter	Median (lower – upper quartile)		
	Control gr. (n = 23)	CKD I (n = 20)	CKD II (n = 41)
Age [years]	10.5 (5.0-16.5)	9.5 (4.0-12.5)	11.0 (4.5-16.5)
Gender	13 girls 10 boys	5 girls 15 boys	17 girls 24 boys
eGFR [ml/1.73m^2/min]	97.1 (92.3-115.0)	79.5 (65.7-97.4)	26.2 (17.3-41.5)

Table 2. Serum concentrations of examined parameters in CKD children and in control group

Parameters in serum	Median (lower – upper quartile)		
	Control gr. (n = 23)	CKD I (n = 20)	CKD II (n = 41)
sMCP-1 [ng/ml]	348.3 (328.9-432.2)	1157.6 [a] (1143.2-1183.7)	994.3 [b] (977.2-1013.0)
sMCSF [pg/ml]	258.2 (253.7-265.0)	874.2 [a] (864.9-895.4)	989.2 [b] (965.4-1031.3)
sMIF [pg/ml]	20.2 (19.4-21.4)	62.0 [a] (61.7-62.4)	67.9 [b] (66.4-70.1)
s neopterin [ng/ml]	23.3 (22.8-23.5)	92.9 [a] (91.8-95.5)	84.5 [b] (82.4-88.0)

- Mann Whitney U test:
- [a] $p < 0.0001$ CKD I vs. control gr. [b] $p < 0.001$ CKD II vs. CKD I

Table 3. Urine concentrations of examined parameters in CKD children and in control group

Parameters in urine	Median (lower – upper quartile)		
	Control gr. (n = 23)	CKD I (n = 20)	CKD II (n = 41)
uMCP-1 [ng/mg creatinine]	88.40 (78.49-101.19)	872.55 [a] (798.40-940.20)	804.40 (658.35-924.83)
uMCSF [pg/ mg creatinine]	1004.37 (963.74-1125.22)	6948.43 [a] (6296.86-7566.25)	5940.79 [b] (5441.79-7464.75)
uMIF [pg/ mg creatinine]	0.87 (0.79-1.08)	3.54 [a] (3.20-3.74)	3.75 (3.36-4.59)
u neopterin [ng/ mg creatinine]	112.31 (101.09-131.57)	300.14 [a] (282.05-324.27)	501.76 [b] (446.26-667.01)

- Mann Whitney U test:
- [a] $p < 0.0001$ CKD I vs. control gr. [b] $p < 0.001$ CKD II vs. CKD I

Table 4. Fractional excretion of examined parameters in CKD children and in control group

Fractional excretion of parameters	Median (lower – upper quartile)		
	Control gr. (n = 23)	CKD I (n = 20)	CKD II (n = 41)
FE MCP-1 [%]	0.18 (0.14-0.19)	0.42 [a] (0.36-0.47)	1.58 [b] (0.89-3.02)
FE MCSF [%]	2.79 (2.63-3.06)	4.40 [a] (3.93-4.93)	11.67 [b] (6.72-21.18)
FE MIF [%]	0.03 (0.02-0.04)	0.03 (0.03-0.04)	0.11 [b] (0.07-0.19)
FE neopterin [%]	4.53 (3.64-5.32)	5.96 (5.36-6.63)	6.49 [b] (4.21-11.80)

- Mann Whitney U test:
- [a] $p < 0.0001$ CKD I vs. control gr. [b] $p < 0.00001$ CKD II vs. CKD I

CONCLUSIONS:

1) Fractional excretion of the examined markers is a useful tool in the assessment of progression of tubular dysfunction in the course of chronic kidney disease.

2) The FE MCP-1 values show that the inflammatory process precedes the tubular damage.

3) FE MCSF and FE neopterin may be considered new markers of renal parenchyma inflammation in the course of CKD.

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