Chapter 3

Dialysate CA125 levels in children treated with peritoneal dialysis.

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ABSTRACT

Peritoneal mesothelial cells are important for the local host defence and membrane integrity. Dialysate CA125 (dCA125) has been shown to be a good marker for the mesothelial cell mass in adult peritoneal dialysis (PD) patients. In children on PD no information is available yet. We measured dCA125 in 65 dialysate samples of 24 PD children with a median age of 9.2 (2-18) years and 2.6 (0.1-9.3) years of PD treatment.

The median dCA125 concentration was 8 (2.3-30.7) U/ml and CA125 appearance rate (CA125AR) 66.5 (18-282) U/min/1.73 m^2. On cross-sectional analysis, a negative correlation was found between dCA125 and duration of PD treatment ($r=-0.3$, $p=0.04$). No relation was found between age and dCA125 or CA125AR when the first measurement from each child was considered. No correlation was found between dCA125 and the mass transfer area coefficient of creatinine ($MTAC_{creat}$). Longitudinal analysis showed a negative trend in CA125AR with duration of PD treatment ($p=0.03$). No relation was found between the peritonitis incidence and dCA125 or CA125 AR.

In conclusion: no influence of age on the dCA125 and CA125AR was found. Levels of dCA125 declined with the duration of PD treatment, reflecting mesothelial cell mass, but they did not correlate with $MTAC_{creat}$ or the peritonitis incidence in stable PD children.

INTRODUCTION

Peritoneal mesothelial cells are important for the local host defence since they are able to produce various cytokines or chemokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) [1,2]. The chemoattractive and stimulating properties of these cytokines result in an influx of neutrophils and macropaghes in the peritoneal cavity and activation of these phagocytes [3]. Loss of mesothelial cells has been reported in some long-term PD patients [4]. Long-term peritoneal dialysis treatment might thus result in an impaired local host defence mechanism [5]. Children treated with PD have a higher peritonitis incidence compared to adults, resulting in more morbidity and treatment failure [6-10] for which a difference in the immune system might be responsible. The uremic state, the loss of mechanical barrier and the not fully developed immune system in children contribute to a susceptibility for infections Cancer antigen (CA) 125 has been shown to be a good marker for mesothelial cell mass or turnover in adult PD patients [11]. Dialysate concentrations of CA125 (dCA125) decreases with the duration of peritoneal dialysis [12]. No relationship between CA125 and peritonitis incidence has been found [13]. One study reported a relationship between dialysate CA125 and peritoneal solute transport [14], but this finding could not be confirmed by others [15]. In children on PD no information on dCA125 has been published yet.

The aim of the present study was to analyze dialysate CA125 concentrations and the appearance rate of CA125 in peritoneal effluent of children treated with PD, with cross-sectional and longitudinal analyses, studying the relationship between CA125 and age, duration of PD treatment, peritoneal transport parameters, peritonitis incidence and mesothelial cell numbers.

PATIENTS AND METHODS

We measured CA125 in 65 dialysate samples of 24 children treated with PD. The median age was 9.2 years (range 2-18) and median duration of PD treatment was 2.6 years (range 0.1-9.3). Dialysate samples were obtained during a standard peritoneal permeability analysis (SPA) using a 4 hour dwell with a 1.36% or 3.86% glucose solution (Dianeal®, Baxter BV, Utrecht, the Netherlands) [16,17]. We performed 1 SPA in six of the children, 2 SPAs in six more, 3 SPAs in another six; 4 SPAs in one child and 5 SPAs in the remaining five children. The median peritonitis incidence was 0.9 episodes per patient year (range 0-6). Cytospins were prepared from 16 children for total cell count and differentiation. Results from the children were compared with results obtained from adult PD patients.

Dialysate samples for the CA125 measurement were taken from a test bag after 4 hours. The samples were centrifuged (500 g, 10 min) and the supernatants stored at -20°C until analysis was performed. Levels of CA125 were measured with a microparticle enzyme immunoassay using a commercially available monoclonal antibody OC125 (Cis Bio International, France) on an Imx autoanalyzer (Abbott Laboratories Imx, North chicago, USA). This method was validated for dialysate measurements in our laboratory [18].

The CA125 AR was calculated as the dialysate CA125 (U/mL) multiplied by the dwell volume (mL), divided by the dwell time (minutes) and corrected for body surface area.

Results are given as medians and ranges. Differences between children and adults were tested with the Mann-Whitney non-parametric rank test. Correlations between duration of PD treatment, age, transport parameters, mesothelial cells and CA125 were tested with the Spearman rank correlation test. A Friedman trend analysis was performed for the longitudinal measurements.

RESULTS

The median dCA125 concentration was 8 U/mL (range 2.3-30.7). The median CA125 AR was 66.5 U/min/1.73 m^2 (range 18-282). No relationship was found between age and dCA125 or CA125 AR when the first SPA measurement of each child was considered. The dCA125 levels were not different in the group with a high peritonitis incidence (1) and the group with a low peritonitis incidence (<1). Furthermore, the peritonitis incidence was not related to the dCA125 levels. No relation could be demonstrated between the mass transfer area coefficient of creatinine ($MTAC_{creat}$) or glucose absorption and dCA125. The restriction coefficient to macromolecules (RC) was negatively correlated with the dCA125 (r=-0.4, p=0.004) and CA125 AR (r=-0.4, p=0.003). When only the first SPA measurement was considered, the relation between the dCA125 or CA125 AR and the RC was not present.

A negative correlation was found between dCA125 concentration and the duration of PD treatment (r=-0.3, p=0.04, Figure 1). The correlation did not reach significance for CA125 AR (r=-0.2, p=0.08).

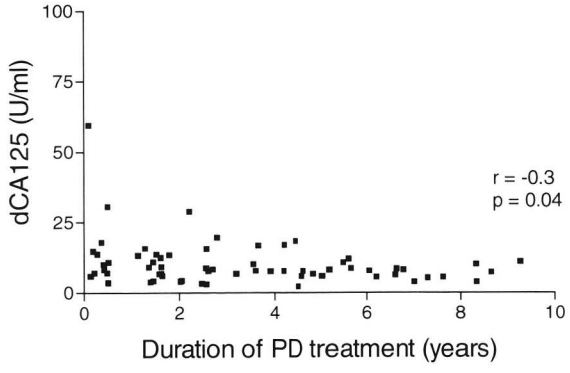

Figure 1. Relation between dialysate CA125 (dCA125) levels in PD children and duration of dialysis treatment.

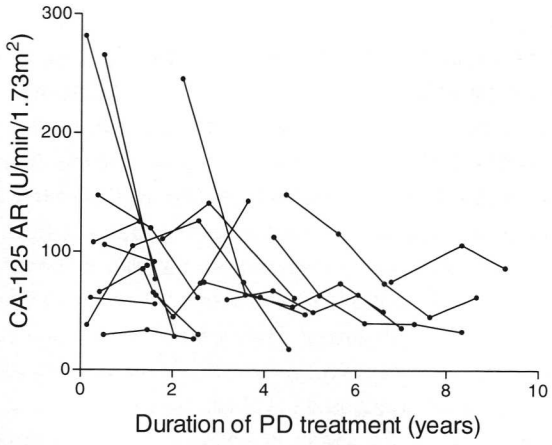

Figure 2. Longitudinal analysis of CA125 appearance rates in the individual PD children.

Figure 2 shows the longitudinal follow-up of each patient. A negative trend of dCA125 and CA125 AR was found with duration of PD treatment (p=0.03).

The percentage of mesothelial cells and the absolute number of mesothelial cells in the cytospins did not decrease significantly with the duration of PD treatment. The dCA125 levels were not related to the absolute mesothelial cell number in the dialysis effluent (data not shown). The CA125 AR had some relationship to the percentage mesothelial cells but this was not significant (r=-0.4, p=0.08, data not shown).

DISCUSSION

The present study showed that dialysate CA125 levels in PD children declines with the duration of PD treatment. This has been demonstrated previously in adult PD patients [12,19]. However, we could not find a significant relationship between mesothelial cell numbers and dCA125 or CA125 AR. This finding is probably caused by the relatively low number of cytospin preparations and the low number of children treated with PD over a long period. No influence of age on dCA125 levels or CA125 AR was found. Also, no differences were present between adult PD patients and children. In PD children the peritoneal transport of small molecular weight solutes such as creatinine as shown by the $MTAC_{creat}$ showed no change with duration of PD treatment; on the other hand, the transport of high molecular weight proteins decreased [17]. The result is an increase in the restriction coefficient, which is a marker for the intrinsic permeability of the peritoneal membrane. This finding may explain the correlation between the restriction coefficient and the dCA125 level in the cross-sectional study. The former parameter increases with the duration of PD treatment, the latter parameter decreases. The relationship was not present when only the first measurement

from each patient was considered. This finding supports our contention that the two parameters are not directly related. The number of peritonitis episodes increases with duration of PD treatment. If the mesothelial cells were a principle factor in the anti-bacterial defence mechanism, the peritonitis incidence should be highest in long-term PD patients with a reduced mesothelial cell mass. However, we could find no relationship between peritonitis incidence and duration of PD treatment. The number of patients that were transferred to hemodialysis treatment and the reason for transfer may have influenced these results. Betjes et al. demonstrated a relationship between a low number of mesothelial cells and a high peritonitis incidence [20], but this finding was not confirmed by others [14]. None of our patients developed a clinical picture of peritoneal sclerosis preceded by a sudden decrease of the dCA125 concentration. No peritoneal membrane biopsies were taken to analyze the influence of membrane changes on dCA125 levels.

We conclude that the dCA125 levels in children treated with peritoneal dialysis decline with the duration of dialysis treatment in a manner similarly to that in adult PD patients. No correlation between the peritoneal clearance of low molecular weight solutes and dCA125 levels were found. A relationship between dCA125 and the restriction coefficient is due to the duration of dialysis treatment. Although the mesothelial cell mass play an important role in the peritoneal immune defense, we could not demonstrate that children with a high peritonitis incidence had dCA125 levels different than those in children with a low peritonitis incidence.

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