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Tumor Markers CA 125 and CA 19-9 in Cord Blood and During Infancy: Developmental Changes and Use in Pediatric Germ Cell Tumors

PEKKA LAHDENNE, SARI PITKÄNEN, JUKKA RAJANTIE, PENTTI KUUSELA, MARTTI A. SIIMES, MARJATTA LANNING, AND MARKKU HEIKINHEIMO

Children's Hospital [P.L., S.P., J.R., M.A.S., M.H.] and Department of Bacteriology and Immunology [P.K.], University of Helsinki, Finland, Children's Hospital, University of Oulu, Finland [M.L.], and Washington University School of Medicine Children's Hospital, Division of Pediatric Hematology-Oncology, St. Louis, Missouri 63110 [M.H.]

ABSTRACT

Tumor markers CA 125 and CA 19-9 are elevated in a variety of malignancies in adult patients, but only little is known of their biology during gestation or infancy. We have addressed the developmental pattern of these carbohydrate antigens in pediatric patients by measuring their serum levels in 133 cord blood samples from the second through third trimester of gestation and in 39 infants aged less than 1.5 y. The serum concentrations of both markers revealed developmental changes, the levels being higher at earlier gestation (wk 24 through 37) than at term or during infancy. The clinical value of the markers was evaluated by monitoring 26 children with germ cell tumors; 14 benign and 2 immature teratomas, and 11 malignant germ cell tumors. Patients with immature sacrococcygeal teratomas showed constant and prolonged elevations of serum CA 125 and CA 19-9. In contrast, all but two children with mature teratomas had normal marker levels; these two patients with abnormally high serum CA 125 and CA 19-9 values for the first 4 postoperative weeks had a benign ovarian and ventricular teratoma, respectively. Of the 11 children with malignant germ cell tumors, serum CA 125 or CA 19-9 concentration was elevated in four patients at diagnosis and declined to normal within 2 wk after institution of therapy. Malignant recurrence in two patients was not associated with a reelevation of the CA 125 level. Taken together, our results demonstrate a developmentally regulated pattern of serum CA 125 and CA 19-9. The carbohydrate markers were usually inferior to α-fetoprotein in monitoring of germ cell tumors, but may be a useful adjunct in the follow-up of immature teratomas. (***Pediatr Res* 38: 797–801, 1995**)

Abbreviations

AFP, α-fetoprotein
SCT, sacrococcygeal teratoma
95% CI, age-dependent 95% confidence interval

Measurements of oncodevelopmental serum tumor markers AFP and placental proteins such as human chorionic gonadotropin are used in the diagnosis and follow-up of patients with malignant germ cell tumors. AFP synthesis correlates with the presence of yolk sac components within the tumor. Of all patients with malignant germ cell tumors, 36–86% have elevated serum AFP concentrations (reviewed in Ref. 1). Analogously, tumors containing trophoblastic elements can be identified by the production of human chorionic gonadotropin.

In addition to extra-embryonic elements, various embryonic structures can be found in germ cell tumors. Therefore, antigens derived from embryonic tissues are of potential value as tumor markers in these cases. CA 125 and CA 19-9 are carbohydrate antigens originally detected by MAb directed against a colorectal and ovarian epithelial carcinoma cell line, respectively (2, 3). The CA 125 and CA 19-9 antigens are found at low concentrations in the sera of healthy adults, but are elevated in patients with ovarian carcinomas and gastrointestinal malignancies (4–9). Only little is known about the role of these markers in childhood malignancies. In children with leukemia and non-germ cell solid tumors, we have reported that the serum levels of CA 125 and CA 19-9 are usually low (10). In another study, CA 19-9 proved not to be a useful tumor marker in 11 adolescents with colorectal carcinoma (11). On the other hand, CA 125 and CA 19-9 are elevated in a subset of children with premalignant and malignant liver diseases (12, 13).

Although CA 125 and CA 19-9 are known to be expressed in fetal tissues (14–16), the ontogenesis of these antigens has not been studied. The serum levels of these markers in infancy have neither been thoroughly explored. The aim of this study

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Correspondence: Markku Heikinheimo, University of Helsinki, Stenbäckinkatu 11, 00290 Helsinki, Finland.
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was to examine the serum levels of CA 125 and CA 19-9 during gestation and infancy. In addition, by taking advantage of our reference values, we illustrate the putative value of these markers in monitoring of children with germ cell tumors.

METHODS

Cord blood samples. Cord blood samples were collected from the Finnish screening program for congenital hypothyroidism (17). Altogether 105 samples from preterm and 28 samples from term infants were included. In the analysis, the samples from preterm infants were divided into two groups according to the gestational age; samples from those born at 24–32 gestational weeks (n = 32) and from those born at 33–37 wk (n = 73) (Table 1). The term infants were born at a mean gestational age of 40 wk (range 38–42 wk).

Reference serum samples during infancy. Serum samples from 39 infants waiting for minor surgical operations were obtained at the ages of 0.1 through 1.5 y. For the statistical evaluation, the samples were divided into two groups; samples from infants aged 0.1–0.5 y (n = 22) and those from infants aged over 0.5 y (n = 17).

Patients with benign teratomas. Sixteen children underwent operation for a benign teratoma between 1985 and 1991 at the Children's Hospital, University of Helsinki, and serial serum samples from these patients were collected for determination of AFP (n = 79), CA 125 (n = 102), and CA 19-9 (n = 112). Four to 24 samples (mean 10 samples) from each patient were available. Ten of the children were operated on at their birth day for a neonatal SCT. Of these 10 children with SCT, the teratoma was histologically immature in two. The other patients included three children with an ovarian, one with a testicular, one with a ventricular, and one with an ocular teratoma. At the time of diagnosis these six children were aged 1 d to 11.4 y (mean 5.0 y). The postoperative follow-up period was for 0.5–5.2 y (mean 2.0 y). Besides the tumor, no other organ disorder was found in any of these 16 patients.

Patients with malignant germ cell tumors. Eleven children were treated for a malignant germ cell tumor between 1985 and 1991 at the Children's Hospitals, University of Helsinki and University of Oulu. At the time of diagnosis these children were aged 9 mo to 12 y (mean 2.6 y). After operative and cytostatic treatment the patients were followed up regularly for 2–6 y (mean 3.5 y). From these 11 patients serial serum samples were collected for analyses of AFP (n = 224), CA 19-9 (n = 78), and CA 125 (n = 86). Five to 30 samples (mean 17 samples) from each patient were available for this study. In all the children with malignant tumors, a thorough workup for other organ disorders performed at diagnosis and during the follow-up was negative.

Tumor marker analyses. Serum concentrations of CA 125, CA 19-9, and AFP were measured by RIA with the sensitivities of 5.6, 6.2, and 1 μg/L, respectively (1, 7, 18). The reference values for AFP concentrations have been reported using the same laboratory conditions (19). For children older than 18 mo, reference values for CA 125 and CA 19-9 reported earlier were used: the upper limits of 95% confidence interval were 16 and 32 U/L, respectively (10).

Statistical methods. Statistical differences between the groups were analyzed by analysis of variance.

This study was approved by the respective ethical committees.

RESULTS

CA 125 and CA 19-9 in cord blood. The mean serum concentrations of CA 125 were dependent on the gestational age of the newborn and were 68, 34, and 10 U/L in cord blood samples from preterm infants born at 24–32 wk, 33–37 wk, and from those born at term, respectively (Fig. 1, Table 1). These differences were also statistically significant (preterm infants born at 24–32 wk *versus* term infants, p = 0.0001; preterm infants born at 33–37 wk *versus* term infants, p = 0.0009: preterm infants born at 24–32 wk *versus* those born at 33–37 wk, p = 0.01).

In infants born at 24–32 wk, 33–37 wk, and at term, the mean serum concentrations of CA 19-9 were 98, 113, and 53 U/L, respectively (Fig. 2, Table 1). Serum concentrations of CA 19-9 in preterm infants born at wk 33–37 were higher than in term infants (p = 0.04), but did not differ between the two preterm groups.

CA 125 and CA 19-9 in infancy. During infancy, the serum concentrations of CA 125 remained at the low level observed in cord blood of term infants. In contrast, serum concentrations of CA 19-9 continued to decrease postnatally (term infants at birth *versus* infants aged 0.1–0.5 y, p = 0.0001), and reached the level reported earlier for older children (10) by the age of 0.5 y.

CA 125, CA 19-9, and AFP in children with benign teratomas. Serum concentrations of CA 125 or CA 19-9 were above the upper limit of age-dependent 95% CI in 4 of the 16

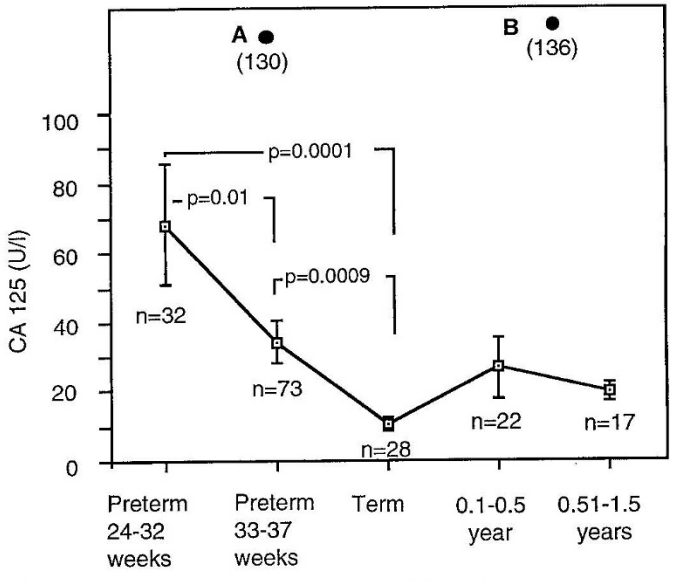

Figure 1. Serum concentrations (mean ± SEM) of CA 125 in preterm and term infants at birth and in infancy. Number of patients studied is given for each age group under the columns. *Closed circles* depict serum values at diagnosis of the patient with immature sacrococcygeal teratoma (born at 36 gestational weeks) and the patient with mature ventricular teratoma at the age of 6 mo.

Table 1. *Serum concentrations of CA 19–9 and CA 125 (mean and upper limit of 95% CI) in preterm and term infants at birth and in infants under 1.5 y of age (U/L)*

Infant group	CA 19–9			CA 125		
	n	95% CI	Mean	*n*	95% CI	Mean
At birth						
Preterm (24–32 wk)	19	179	98	32	103	68
Preterm (33–37 wk)	59	150	113	73	47	34
Term (38–42 wk)	28	70	53	28	14	10
Postnatal						
0.1–0.5 y	22	42	30	22	45	25
0.51–1.5 y	17	24	19	17	25	20

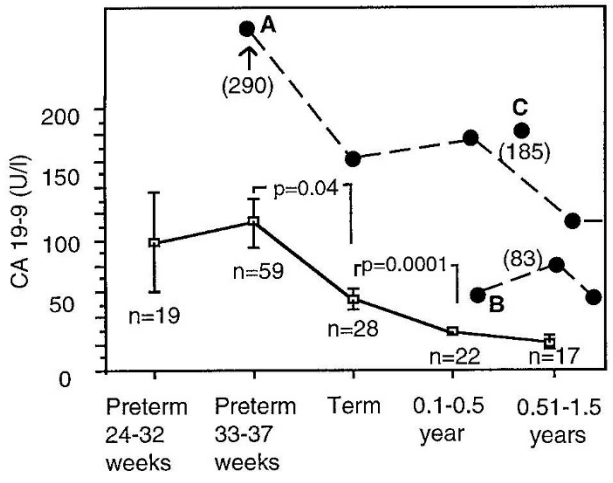

Figure 2. Serum concentrations (mean ± SEM) of CA 19-9 in preterm and term infants at birth and in infancy. Number of patients studied is given for each age group under the columns. *Closed circles* connected with dotted lines depict serial serum values of the two patients with immature sacrococcygeal teratomas born at 36 gestational weeks (*A*) and born at term (*B*), and serum CA 19-9 at diagnosis of a patient with mature ventricular teratoma at the age of 6 mo.

children with benign teratomas; two immature SCT, one ventricular teratoma, and one ovarian teratoma (Table 2, Figs. 1 and 2). The two patients with an immature teratoma showed prolonged elevations of these markers, although in one of them CA 19-9 and CA 125 at birth levels had been within the reference range.

In all 16 patients with benign teratomas, serum concentrations of AFP remained within the age-dependent reference values throughout the follow-up period. Based on elevations in the AFP levels, malignant recurrences were suspected in the two patients operated on for immature SCT; no recurrences were, however, found in these two or in any of the other patients.

CA 125, CA 19-9 and AFP in children with malignant germ cell tumors. Four of the 11 patients with malignant germ cell tumors showed elevated serum concentrations of CA 125 or CA 19-9 during follow-up (Table 2). In 10 patients, serum AFP was elevated, ranging from 430 to 179,000 μg/L (mean 40,760 μg/L) at diagnosis. In a 2-y-old boy with a sacrococcygeal yolk sac tumor and elevated serum APF and CA 125 level at diagnosis, a malignant recurrence was associated with elevated AFP, but normal CA 125 levels. A 2-y-old boy operated on for a testicular embryonal carcinoma had serum CA 125 levels fluctuating at two to four times the upper 95% CI for 3 months postoperatively; the patient remained disease-free during the follow-up. Serum CA 19-9 was elevated (2.9 times 95% CI) at diagnosis in one patient with an ovarian embryonal carcinoma, and CA 125 (4.8 times 95% CI) in another patient; malignant recurrence in the latter patient was not associated with an elevation of any of the markers studied.

DISCUSSION

CA 125 and CA 19-9 are expressed in fetal tissues (14–16), but serum concentrations of these antigens at various gestational ages or during infancy have not been studied earlier. During fetal development the CA 125 antigen is localized to the amnion, derivatives of Müllerian epithelium, *e.g.* endometrium, endocervix, and Fallopian tube and coelomic epithelium, including the peritoneum, pleura and pericardium (14, 16). Expression of the antigen on these developmental sites is maintained through adulthood, resulting in the presence of low serum levels of CA 125 in all non-tumor-bearing adults (20). Elevated levels of CA 125 are found in patients with diseases, benign or malignant, affecting these tissues (8). High serum CA 125 levels in pregnant women (7, 21) and abundant levels of CA 125 in amniotic fluid (22) further demonstrate that CA 125 antigen is expressed during normal growth and development. It can be speculated that the high serum levels of CA 125 during gestation observed in the present study may be caused by the rapid fetal growth of tissues and organs. On the other hand, because circulating glycoproteins are largely cleared by the liver (23), immaturity of hepatic function in preterm infants may also increase the serum levels of CA 125. Impairment of the liver function or malignant changes in the liver is also associated with elevated serum CA 125 in a subset of patients with hereditary tyrosinemia and hepatoblastomas (12, 13). CA 19-9 is not as widely distributed as CA 125 during fetal life. Raux *et al* (15) detected this antigen in the fetal gastrointestinal tract but not in other fetal organs. The CA 19-9 antigen has been detected only in trace amounts in normal adult digestive organs (15), but the tissue expression and serum concentrations of this antigen are increased in malignant gastrointestinal diseases (9, 24). For this reason, CA 19-9 has been viewed as an oncofetal antigen for gastrointestinal tract, although it is obviously not organ- or tumor-specific (25, 26). Our findings of elevated but declining serum levels of CA 19-9 toward the end of gestation support the concept of oncofetal character of this antigen.

Table 2. *Children treated for benign or malignant germ cell tumors with elevated serum levels of CA 19–9 and/or CA 125 (the upper limit of age-dependent 95% CI of serum CA 19–9 and CA 125 is given in parentheses under each serum value)*

Patient age at diagnosis	Histologic diagnosis	Location	At diagnosis: CA 19–9 (U/L)	At diagnosis: CA 125 (U/L)	At diagnosis: AFP (μg/L)	Remarks
Benign tumors						
1 d (born at 36 gest wk)	Immature teratoma	Sacrococcyx	290 (150)	130 (47)	51 270	CA 19–9 80–170 U/L for 3 y. CA 125 normal 1 wk postoperatively
1 d	Immature teratoma	Sacrococcyx	26 (70)	33 (14)	40 665	CA 19–9 55–83 U/L, CA 125 25–47 U/L between 6 and 15 mo of age
6 mo	Mature teratoma	Ventricle	185 (42)	136 (25)	58	CA 19–9 and CA 125 normal 4 wk postoperatively
11 y	Mature teratoma	Ovary	270 (32)	84 (16)	2.5	CA 19–9 and CA 125 normal 4 wk postoperatively
Malignant tumors						
2 y	Yolk sac tumor	Sacrococcyx	27 (32)	71 (16)	179 000	CA 125 normal in 2 wk postoperatively. Malignant recurrence 8 mo later: AFP 118 μg/L, CA 19–9 and CA 125 normal
2 y, 3 mo	Embryonal carcinoma	Testicle	10 (32)	38 (16)	521	CA 125 32–70 U/L 3 mo postoperatively
2 y, 6 mo	Embryonal carcinoma	Ovary	<6.2 (32)	77 (16)	<9	CA 125 normal in 2 wk postoperatively. Malignant recurrence 1 y later: CA 125, CA 19–9, and AFP low
12 y	Embryonal carcinoma	Ovary	93 (32)	Not done	25 500	hCG 49 000 IU/L at diagnosis, CA 19–9 normal in 2 wk postoperatively

The reference values during late gestation and infancy, demonstrated in this work, form the basis for the potential use of CA 19-9 and CA 125 in the diagnosis and follow-up of patients with neonatal neoplasia. These markers may be elevated in children with some embryonal tumors such as hepatoblastomas (13) as well as in hereditary tyrosinemia, a premalignant liver disease (12). Serum CA 125 was also found to be elevated in children with abdominal Burkitt's lymphomas (10). CA 19-9 and CA 125 may thus have a role in the follow-up of patients with specific childhood malignancies. SCT are of special interest, because these tumors may give rise to malignant recurrences even when originally benign (27, 28). In the present patients with mature SCT, CA 125 and CA 19-9 were exclusively within reference limits in infancy. In contrast, the patients with immature teratomas showed prolonged elevations of both markers studied. No malignant recurrences, however, were noted in these children. Therefore, it cannot be answered whether CA 125 and CA 19-9 would be useful in predicting early malignant recurrences of immature teratomas. Four patients with malignant germ cell tumors showed elevated levels of CA 19-9 or CA 125 at diagnosis. Malignant recurrences in two of these did not elevate the serum levels of either antigen. Thus, the enhanced expression of CA 125 and CA 19-9 in patients with immature teratomas may rather reflect immaturity than malignant behavior of the tumors. No other organ abnormalities than the tumor were detected in our patients; thus elevated values were not due to any other medical condition described to be associated with elevated serum carbohydrate antigens (14, 16).

Developmental changes in serum levels of tumor markers CA 125 and CA 19-9 were observed during late gestation and infancy adding to the evidence for their oncofetal character. These markers did not prove useful as diagnostic markers for all children with germ cell tumors, but may be of value in the follow-up of patients with elevated serum levels at diagnosis. In comparison with AFP, the classic tumor marker of germ cell malignancies, CA 125 and CA 19-9 proved to be inferior. These markers were, however, elevated in immature teratomas, and determination of CA 125 and CA 19-9 may give additional information during the follow-up of these children.

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