CEA, CA125 AND CA19-9 LEVELS IN CONGENITAL GASTROINTESTINAL ANOMALIES*

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Preoperative and postoperative serum samples of 35 patients with different congenital gastrointestinal anomalies were analyzed for the markers CEA, CA 125 and 19-9 by immunoradiometric assay during a period of three years. The majority of the anomalies were aganglionic megacolon and hypertrophic pyloric stenosis. CA 125 and CA 19-9 were likely to indicate logistic model probabilities for babies with anomalies, while CEA was not ($F=35.78$, $p<0.05$ for CA CA 125 and $F=4.36$, $p<0.05$ for CA 19-9). Probability of no congenital anomaly for babies was:

$$p\ (Normal)=e^{4.41-0.13CA125-0.05CA19-9}/1+e^{4.41-0.13CA125-0.05CA19-9}$$

Using CA 125 as a marker, babies with congenital anomalies were determined with 83.3 percent probability ($F=11.33$, $p<0.05$). On the other hand, it was not possible to predict the type of anomaly with these three markers. CEA, CA 125 and CA 19-9 seem to be prognostic variables associated with congenital anomalies. These biological markers provide information that can be incorporated into the diagnosis of anomalies but without doubt results of markers should be supported by clinical findings.
Key words: tumor markers, anomalies, radioimmunoassay.

Tumor marker production is a reflection of the synthesis and secretion capability of the tumor, the rate of cellular growth, necrosis and programmed cell death[1]. Therefore, tumor markers play an important role in the assessment of patients with some types of malignant tumors[2]. These are not, however, specific markers that precisely predict the occurrence of a particular disease and furthermore, they may be increased in nonmalignant conditions as well[3].

In gastrointestinal tumors, the tumor markers CEA and CA 19-9 are accepted as markers and are usually increased. These markers are very useful in detection of postoperative recurrences and metastases. They are specific but are also detectable in different tumoral processes. Serum from patients with

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gastrointestinal carcinoma often contains increased CA 19-9 concentrations[4]. Increases in the serum concentrations of CEA have been associated with progression of cancers of the gastrointestinal tract, lung and breast. Despite its ubiquitous application as a tumor marker, CEA may be increased in patients with benign diseases of the same organs[5]. Many so-called markers currently used do not discriminate well enough between benign and malignant cells.

The value and distribution of tumor markers in congenital anomalies have not been sufficiently investigated. One can expect some changes of gastrointestinal tumor markers such as CEA and CA 19-9 in babies with congenital gastrointestinal anomalies.

On the other hand, CA 125, which is adequate as a marker for monitoring patients with known ovarian cancer and even for discriminating malignant from benign pelvic masses, has been suggested as an abnormal secretory product from the genital tract and organs[6]. Many factors like pregnancy, menstruation, benign gynecological diseases, and pleural and peritoneal inflammation can lead to increases of CA 125[7,8]. Increased concentrations of CA 125 can also be found in patients with various gastrointestinal malignancies[9].

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genital tract and organs[6]. Many factors like pregnancy, menstruation, benign gynecological diseases, and pleural and peritoneal inflammation can lead to increases of CA 125[7,8]. Increased concentrations of CA 125 can also be found in patients with various gastrointestinal malignancies[9].

We planned this study to investigate the distribution of these three gastrointestinal related tumor markers in congenital gastrointestinal anomalies.

Material and Methods

Patients

Thirty-five babies (23 males and 12 females; mean age 129±25 days) with congenital gastrointestinal anomalies were studied for a period of three years. All patients were evaluated by physical examination, ultrasonography and X-ray studies. The mean age of the mothers of babies with anomalies was 25.2 years. Sixteen males and eight females served as controls. The blood samples of these normal babies and their mothers, with a mean age of 26.3 years, were collected 123±30 days after delivery.

The study protocol conformed to local ethical standards and the Helsinki declaration of 1975, as revised in 1983.

Samples

Venous blood (3 ml) was collected from each patient pre- and postoperatively (4 weeks after the operation) for the measurement of serum tumor marker levels, into plain glass tubes. The serum sample was allowed to clot for 20 minutes then centrifuged at 1000 g for 10 minutes and stored at -20 °C until analysis. We also collected venous blood into plain glass tubes from age and sex-matched control subjects who did not have congenital anomalies. We centrifuged and stored the samples as previously described. Analysis was performed within one month after collection.

Analyses

We performed the following analyses on the samples from patients and controls: serum CEA, CA 19-9 and CA 125 levels were measured with solid phase two-sites immunoradiometric assays employing monoclonal antibodies (Cis biointernational, France).

Following the formation of the coated antibody/antigen/iodinated antigen sandwich, the unbound tracer was easily removed by a washing step. The radioactivity remaining at the tube wall was measured by gamma scintillation counter. Intraassay precisions were 4 percent, 7 percent, and 5 percent respectively.

Statistical Analysis

Student's paired t-test was used to assess the significance of any differences in serum tumor marker concentrations of the preoperative and postoperative babies with congenital gastrointestinal anomalies and of controls. Stepwise logistic regression analysis was used to assess the significance of CA 125, CEA and CA 19-9 levels in determination of congenital anomalies. Specificity of the markers for anomalies was determined with Stepwise discriminant analysis.

Results

Table I lists the characteristics of the study group of 24 normal babies and 35 babies with congenital anomalies.

Table I: Characteristics of 35 Babies with Various Congenital Gastrointestinal Anomalies

	n (Female, Male)	Age, Days±SD	Type of Anomaly
Baby with anomaly	9 (4,5)	124±23	Congenital aganglionic megacolon
	2 (1,1)	150±24	Esophageal atresia
	8 (1,7)	115±30	Congenital hypertrophic pyloric stenosis
	2 (1,1)	130±38	Gastrochisis
	5 (2,3)	138±20	Intestinal atresia
	5 (1,4)	140±26	Anal atresia
	1 (0,1)	110±21	Omphalocele
	3 (2,1)	130±17	Ectopic anus
Baby without anomaly	24 (9,15)	123±30	

When tumor marker levels in preoperative babies were compared with the concentrations in control subjects, babies with anomalies had significantly higher concentrations than the controls ($p<0.05$). Though it was not statistically significant, serum tumor marker levels tended to decrease with operation, and the concentrations of patients were not significantly higher than those of controls after the operation (Fig. 1). When tumor marker levels in mothers of babies with anomalies were compared with those of normal babies' mothers, CA 19-9 and CEA levels were increased, but there was not a statistically significant difference (Fig. 2).

With Stepwise logistic regression analysis, CA 125 and CA 19-9 were likely to indicate logistic model probabilites for babies with anomalies, while CEA was not ($F=35.78$, $p<0.05$ for CA 125 and $F=4.36$, $p<0.05$ for CA 19-9).

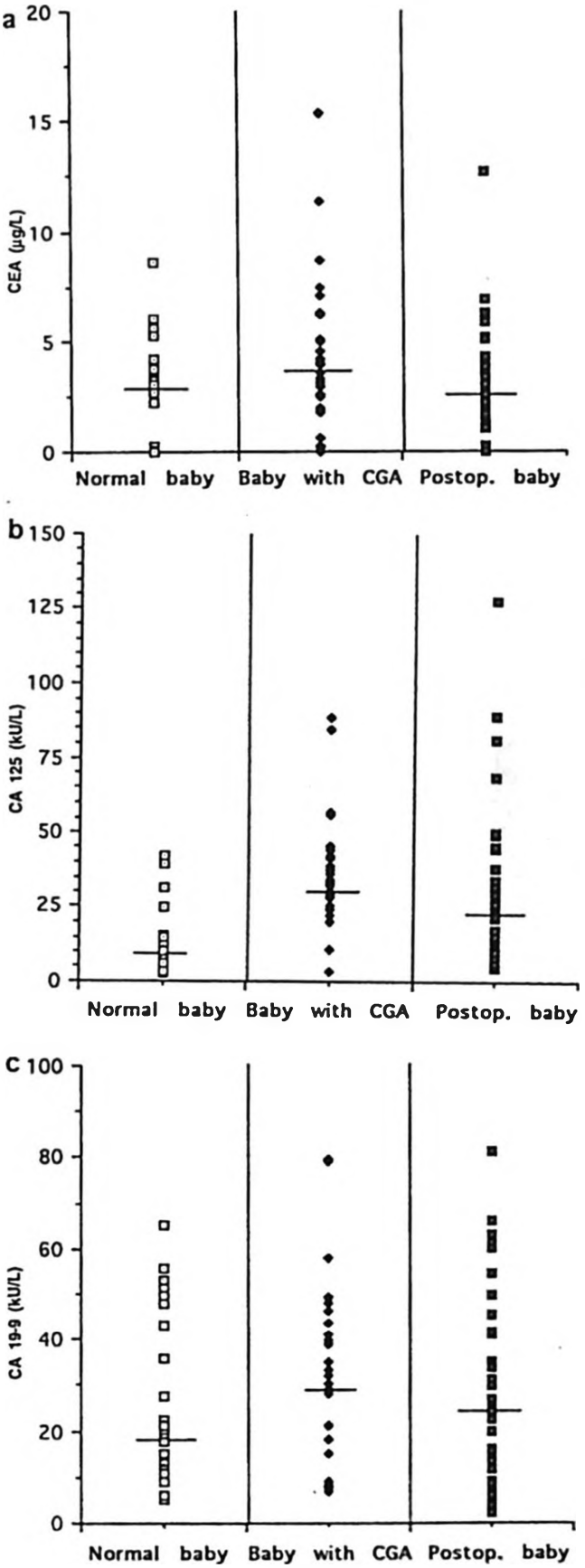

Fig. 1: Serum a) CEA, b) CA 125 and c) CA 19-9 concentrations in babies with congenital gastrointestinal anomalies preoperatively (◆) $p<0.05$, postoperatively (◘) $p>0.05$ and in age- and sex-matched controls (⊡). CA: congenital gastrointestinal anomalies. Horizontal lines indicate the median values.

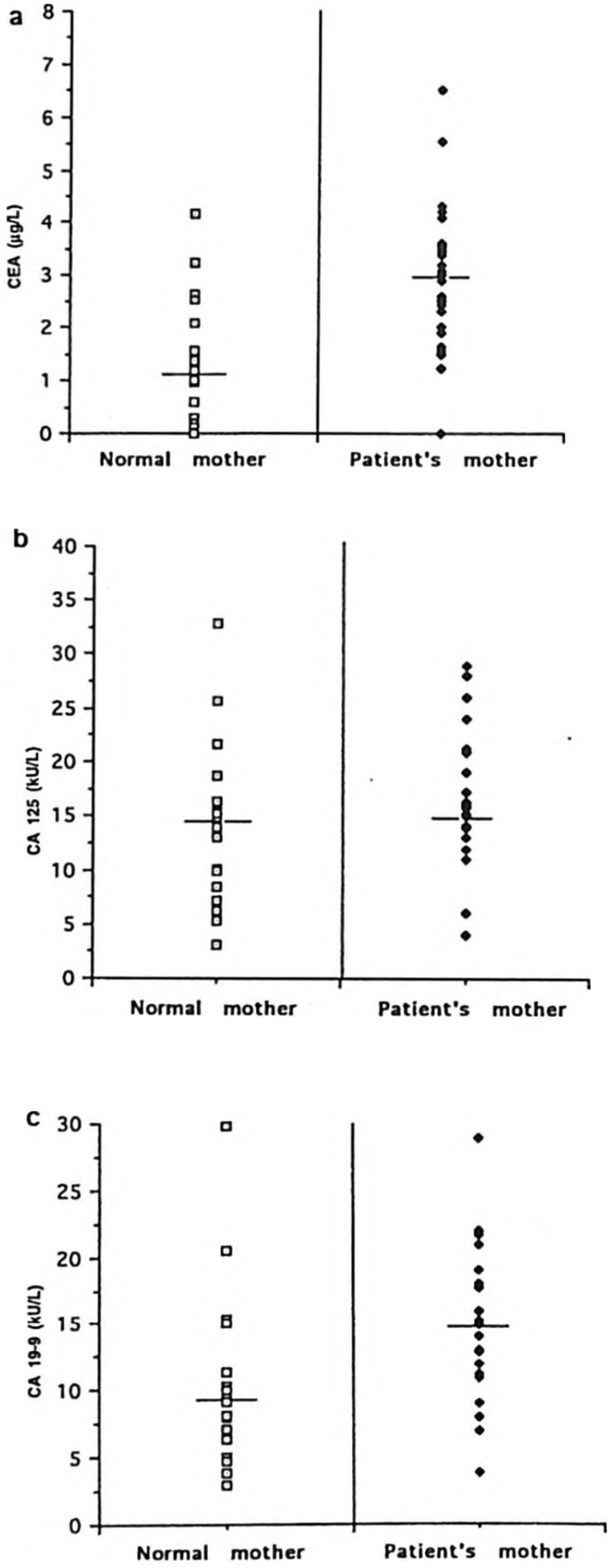

Fig. 2: Serum a) CEA, b) CA 125 and c) CA 19-9 concentrations in mothers of babies with congenital gastrointestinal anomalies (◆) p>0.05 and in mothers of control babies (⊡). Horizontal lines indicate the median values.

Probability of no congenital anomaly for babies was;

$$p\ (Normal)=e^{4.41-0.13CA125-\ 0.05CA19-9}/1+e^{4.41-0.13CA125-\ 0.05CA19-9}$$

Specificity of the markers for anomalies was determined with Stepwise discriminant analysis. This analysis was performed for babies with aganglionic megacolon and hypertrophic pyloric stenosis, as the number of babies in the other groups was not high enough for discriminant analysis. Thus, the relationship of marker level with type of anomaly was investigated in normal babies and babies with aganglionic megacolon and hypertrophic pyloric stenosis; mean marker levels in these anomalies and control babies are shown in Table II. It was found that, when using CA 125 as a marker, babies with congenital anomalies were determined with 83.3 percent probability ($F=11.33$, $p<0.05$).

Table II: Relationship Between Type of Anomaly and Serum Concentrations of CEA, CA125 and CA19-9

	Mean (SD)		
	CEA, ug/L	CA125, kU/L	CA19-9, kU/L
Congenital aganglionic megacolon (n=9)	4.57 (4.6)	42.75 (25.81)	46.43 (22.01)
Congenital hypertrophic pyloric stenosis (n=8)	3.37 (2.52)	29.29 (18.89)	37.75 (9.38)
Normal babies (n=24)	2.36 (2.39)	12.83 (10.89)	28.37 (23.07)

It was possible to classify aganglionic megacolon patients (44.4%) and hypertrophic pyloric stenosis patients (12.5%). In total, 61 percent were classified correctly.

Discussion

We observed that tumor marker levels were affected in congenital anomalies, as babies with anomalies had significantly higher concentrations of tumor markers than controls ($p<0.05$). Tumor markers lack specificity in that they are present or increased in subjects with benign disease or even in normal individuals[3,5]. These are not truly cancer-specific substances. Tumor markers are usually due to differentiation during fetal life and thus are oncofetal antigens. We suggest that the increased levels of tumor markers indicate the patient's work-up should include an assessment of non-neoplastic disease. Congenital anomalies seem to be one of the conditions in which tumor markers are increased. It is also possible that babies with anomalies are more susceptible to carcinogenesis when they grow older. According to Potter's[10] deletion hypothesis, cytoplasmic reactions may control cell division; carcinogens may cause loss of these control reactions. It is obvious that control of cell division is lost in congenital anomalies. The Vogelstein hypothesis[11] incorporates the proposal that most colorectal carcinomas arise from preexisting benign adenomas. Congenital anomalies in which control of cell division has been lost may contribute to the development

of colorectal carcinomas. Such reasoning suggests that further research on cancer incidence in babies with anomalies should be encouraged, as chromosomal changes and point mutations are crucial events in both carcinogenesis and anomalies and lie at the heart of all current genomic models.

CA 125 and CA 19-9 were increased in babies with anomalies, and these variables indicated the logistic model probabilities of having anomalies. Increases of CEA in serum were seen in benign and malignant diseases of the pancreas, colon, liver, lung and breasts[5], but it did not increase in babies with congenital anomalies. Assuming that assessment of marker in mothers could provide valuable information, measurements were also performed using sera of mothers. CEA and CA 19-9 levels were increased in mothers of ill babies when compared with those of normal babies' mothers, but there was not a statistically significant difference, suggesting that these markers cannot be used to monitor development of congenital gastrointestinal anomalies. Whether the marker levels of mothers increased during pregnancy and birth remains to be determined.

The effects on CA 125 in babies were more pronounced than effects on the other two markers. One can expect placental crossing of the CA 125 antigen, but its natural half-life in serum was estimated at 4.8 days[12]. Thus, maternal transfer due to pregnancy or to benign gynecologic problems present in the mothers of this group was ruled out. Appropriate timing of blood collections for tumor marker assays is crucial, so blood was collected from babies when they were 129±25 days old, taking into account the half-lives of markers. Again, the high tumor marker values, which could be due to their necrotic releases after operation which were erroneously reported as false-positive increases, was ruled out by collecting the samples four weeks' postoperatively. Blood samples were also taken postoperatively in the hope of using results as a marker for monitoring disease course. Venous sera of babies were collected four weeks after operation. Though serum tumor marker levels tended to decrease with operation, this was a statistically nonsignificant difference when compared with preoperative values. One reason for this may be the need of a second operation for some babies. It was reported that tumor marker levels which do not return to normal are reflective of residual disease[13,14]. It is also possible that markers will return to normal after a longer period of time.

Tumor markers were thought to be increased in malignancies due to cellular proliferation. When we classified our patients as having proliferative or atretic anomalies, there was no difference in tumor marker values of these two groups.

CEA, CA 125 and CA 19-9 seem to be prognostic variables associated with congenital anomalies. In the future, risk factors and markers will be used, to determine who is destined to develop diseases. Although this study may not yet confirm the use of markers in early detection of congenital anomalies, we

believe there is a need for studies on this subject so that use of these markers as criteria for congenital anomaly diagnosis would be justified by available information. Aside from the issue of cost, standardization of these serum assays is well advanced and interlaboratory reproducibility has been steadily improving. There are no complications in this type of diagnosis, and these biological markers provide information that can be incorporated into diagnosis of anomalies. Still, there is no doubt that marker results should be supported by clinical findings.

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