The incidence of congenital malformations in children with cancer

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We evaluated the incidence of congenital malformations in 566 children (median age: 8, M:F 1.3) with lymphomas and solid tumors using patient records. In this study, 12.7% of children either had a congenital malformation (7.8%) or a birthmark (4.9%). The incidence of patients with a childhood cancer syndrome was 3% and these cases developed typical tumors. The rate of consanguineous marriages was 12.6%, and family history of cancer was positive in 31.2%. Median age at cancer diagnosis, gender, maternal age, history of stillbirth and missed abortion, consanguinity of parents, and family history of cancer were not significantly different in cases with and without a congenital malformation. The most frequent cancers were central nervous system tumors and lymphomas. No remarkable association between a particular anomaly and a specific cancer type could be shown. The high incidence of congenital anomalies in this study may stimulate future large cohort studies in our country.

Key words: congenital malformation, birthmarks, childhood cancer, childhood cancer syndromes.

The presence of cancer and a congenital malformation in the same child may be explained in certain cases by an underlying genetic abnormality. A congenital malformation, also referred to as a congenital anomaly, is a permanent physical defect present in a baby at birth, irrespective of whether the defect is caused by a genetic factor or by prenatal events that are not genetic. There is evidence of an increased risk of cancer in children with genetic disorders and also with congenital malformations[1-5]. A markedly increased risk of cancer in children with some genetic syndromes, chromosomal anomalies, and congenital malformations has been widely recognized[6-12]. There are also a limited number of studies suggesting that even children with minor malformations or variants, including birthmarks, may have an increased risk of cancer, and that these could be a marker of "altered" prenatal development[13-16]. A birthmark is a blemish on the skin formed before birth. The cause of birthmarks is unknown, and some types seem to run in families. A number of different types of birthmarks are known that include, but are not limited to, stork bites, Mongolian blue spots, strawberry marks, café-au-lait spots, congenital melanocytic nevi, and port-wine stains.

The cumulating data on the relation of minor and major congenital malformations and birthmarks may provide an opportunity to investigate the basic mechanisms of both tumorigenesis and development.

In this study, we aimed to define the incidence of congenital anomalies and birthmarks in our patients with childhood cancer.

Material and Methods

The patient records for children and adolescents with lymphomas and solid tumors who had been diagnosed and treated in our Pediatric Oncology Department between July 1988

and July 2007 were analyzed retrospectively. Childhood leukemia could not be included since these patients were managed by our Hematology Department. The epidemiological data on demographics, including parents' ages at the time of the child's birth, parental consanguinity, family history of cancer, and medical conditions, were retrieved from the medical records.

All patients referred to the pediatric oncology unit have a detailed physical examination at the time of initial cancer diagnosis and observed congenital abnormalities, if any, are expected to be noted. Patients who were diagnosed with a specific syndrome before the diagnosis of cancer are always re-evaluated to determine if this diagnosis is correct.

These physical examination records were evaluated for this study for the presence of any congenital anomaly and/or birthmark. The reports of radiological investigations (chest X-ray, abdominopelvic ultrasonography (US) and computed tomography (CT), thoracic CT, magnetic resonance imaging (MRI) of the primary and metastatic tumor sites) and echocardiography findings performed throughout the treatment and follow-up period were also assessed, whenever available, for any detected congenital anomaly. Any phenotypic abnormalities that may have been caused by the tumor or the treatment, such as microcephaly after cranial irradiation, were not scored.

The congenital malformations available in the patient records were classified according to the ICD 10, Version 2007 "Congenital malformations, deformations and chromosomal abnormalities", Chapter XVII[17]. Some anomalies and birthmarks documented in our series, which were not included within congenital malformations in this classification system, were also analyzed separately. Birthmarks that resembled a component of a particular syndrome, like café-au-lait in patients with neurofibromatosis (NF)1, were not included in the analyses as "birthmarks".

Statistics

The median age at the time of cancer diagnosis and median maternal and paternal ages at the time of the child's birth in patients with and without anomalies were compared using Student t test. Sex ratios and age groups of patients, consanguinity of parents, and family history of cancer were compared in both groups using chi-square test. Maternal fertility history (abortus, stillbirth) were compared in both groups by Fisher's exact test. Statistical analysis of this study was done using SPSS version 11.0. A difference was considered statistically significant if the two-tailed p-value was <0.05.

Results

The hospital records and the pediatric oncology department records of 573 children with lymphomas and solid tumors seen in our department between July 1988 and July 2007 were evaluated to collect data about the presence or absence of congenital anomalies and about the kind of malformation, if any. The relevant data was available for 566 cases. Seven patient records were excluded because of missing data. The study group consisted of 317 (56%) boys and 249 (44%) girls, and M: F ratio was 1.3. The median age of diagnosis was 8 years (0-20). Table I shows the number of patients with and without malformations and/or birthmarks.

Table I. Distribution of Patients According to the Existence of an Anomaly

Patients	No of pts
Pts without anomaly	494 (87%)
Pts with anomaly	72 (13%)
ICD 10+ CMs	32
ICD 10+ and ICD 10- CMs	4
ICD 10+ and ICD 10- CMs and BM	1
ICD 10+ CMs and BM	3
ICD 10 – CMs	4
BMs	28
Total	566 (100%)

Pts: Patients. CMs: Congenital malformations. BMs: Birthmarks. ICD 10+: Congenital malformations, deformations and chromosomal abnormalities included in ICD 10, Q00-Q99; ICD 10–: Anomalies not included in ICD 10, Q00-Q99.

Table II shows some epidemiologic and familial characteristics in patients with or without anomalies. The overall rate of consanguineous marriages in 566 patients was 12.6%. The family history of cancer was positive in 177 of 566 cases (31.2%). Median age at cancer diagnosis, gender, maternal age at the child's birth, history of stillbirth and missed abortion, consanguinity of parents, and family history of cancer were not different between these

Table II. Some Patient Characteristics

	Patients with CMs and/or BMs	Patients without CMs and/or BMs	p
Number of patients (%)	72 (13)	494 (87)	
Age at cancer diagnosis median (range)	9 (0-18)	8 (0-20)	0.61
Gender			
Male	41 (56%)	277 (56%)	
Female	31 (44%)	218 (44%)	0.86
Parents' ages at child's birth median (range)			
Maternal	24 (16-44)	25 (13-48)	0.14
Paternal	28 (17-48)	30 (16-50)	0.02
Consanguinity of parents	9 (12.7 %)	61 (12.3%)	0.76
Family history of cancer	26 (37%)	151 (31%)	0.39
Maternal fertility history			
Abortus	4 (5.6%)	25 (5%)	0.77
Stillbirth	2 (2.8%)	2 (0.4%)	0.08

CMs: Congenital malformations. BMs: Birthmarks.

two groups (Table II). Maternal age at birth was further analyzed as ≤35 years and >35 years. The incidence of malformations did not show any significant difference between these two maternal age groups (p=0.591). Only the father's age at birth showed a difference between patients with or without anomalies (p=0.02). The paternal age was higher in the group without documented anomalies (Table II). The type and incidence of documented congenital malformations included in ICD 10, Version 2007 are given in Table III. "Other congenital malformations –ICD 10: Q80 – 89" was found to be the most common (40%) type of anomaly in our patients. Within this group of anomalies, NF was the most frequent anomaly (9 patients with NF type 1 and one patient with NF type 2), constituting 21% of all the ICD 10-coded congenital malformations. "Congenital malformations of eye, ear, face and neck- ICD 10: Q10 – Q18" (17%) and "Congenital malformations of genital organs-ICD 10 code: Q50 – 56" (12.5%) were the other most common anomalies.

Other anomalies and birthmarks documented in our patient records that were not coded as "congenital malformations" in the ICD 10 system are shown in Table IV.

Birthmarks were documented in 28 cases. There were 22 records of café-au-lait, 14 non-neoplastic nevus and 1 hypopigmented macule within this group.

The majority of children, 36 cases (82%), had only 1 type of anomaly, 4 (9%) children had 2 anomalies, and the remaining 4 (9%) children had ≥3 anomalies. The maximum number of anomalies for 1 child was 4.

In this study group, 44 (7.8%) patients had a congenital anomaly and 28 (4.9%) had birthmarks. Thus, a total of 72 out of 566 patients (12.7%) had either a congenital malformation and/or a birthmark.

Defined Syndromes

The incidence of patients with a defined syndrome was 3% in 566 children with cancer. There were five clinically proven syndromes in 15 patients: NF1 (n: 9), NF2 (n: 1), tuberosclerosis (n: 2), xeroderma pigmentosum (n: 2), and von Hippel-Lindau syndrome (VHL) (n: 1). These 15 patients accounted for 34% of all patients assigned to have a congenital anomaly (n: 44), and 21% of the patients assigned to have either a congenital anomaly and/or a birthmark (n: 72). Additionally, 2 children had complex isolated hemihyperplasia (IHH) (involvement of half of the body and face). Although they did not fulfill the criteria for typical Beckwith-Wiedemann syndrome (BWS) and should be screened for alterations of the 11p15 region before a definitive diagnosis, IHH may be part of the BWS spectrum. As these two patients typically presented with Wilms tumor, we included these cases within the "overgrowth syndromes".

Table III. Incidence of Congenital Malformations According to ICD 10, Version 2007

Type of malformation	ICD-10 code	No. of patients	%
CMs of the nervous system	Q00-Q07	1	2.1
Microcephaly	Q02	(1)	
CMs of eye, ear, face and neck	Q10-Q18	8	16.7
CMs of eyelid	Q10.3	(1)	
Microphthalmos	Q11.2	(1)	
Congenital cataract	Q12.0	(2)	
Congenital deafness	Q16.9	(1)	
Low-set ears	Q17.4	(1)	
CM of ear, unspecified	Q17.9	(1)	
CM of face, unspecified	Q18.9	(1)	
CMs of the circulatory system	Q20-28	2	4.2
Congenital pulmonary valve stenosis	Q22.1	(1)**	
Congenital stenosis of aortic valve	Q23.0	(1)	
CMs of the respiratory system	Q30-34	2	4.2
CM of nose, unspecified	Q30.9	(2)	
Cleft lip and cleft palate	Q35-37	2	4.2
Cleft palate with cleft lip	Q37.9	(2)	
Other CMs of the digestive system	Q38-45	2	4.17
High-arched palate	Q38.5	(2)	
CMs of genital organs	Q50-56	6	12.5
Undescended testicle, unilateral	Q53.1	(2)	
Hypospadias, unspecified	Q54.9	(3)	
Hypoplasia of penis	Q55.6	(1)	
CMs of the urinary system	Q60-64	1	2.1
Horseshoe kidney	Q63.1	(1)	
CMs and deformations of the musculoskeletal system	Q65-79	5	10.4
Talipes equinovarus	Q66.0	(1)	
Facial asymmetry	Q67.0	(1)	
Syndactyly, webbed fingers	Q70.1	(1)	
Genu varum	Q74.1	(1)**	
Frontal bossing	Q75.8	(1)	
Other CMs	Q80-89	19	39.6
Xeroderma pigmentosum	Q82.1	(2)	
Abnormal palmar creases	Q82.8	(1)	
Accessory nipple	Q83.3	(1)	
Phakomatoses, Neurofibromatosis	Q85.0	(10)	
Phakomatoses, Tuberous sclerosis	Q85.1	(2)	
Overgrowth syndromes	Q87.3	(2)	
von Hippel-Lindau	Q85.8	(1)	
Total		48*	100

Children with multiple anomalies were assigned to all of their diagnosed anomaly groups.

ICD-10: International Classification of Diseases –Version 2007.
CM : Congenital malformation.

*Five patients had multiple congenital anomalies.
**Patients with congenital anomalies and birthmarks.

Table IV. Other Documented Anomalies and Birthmarks

Other congenital anomalies and birthmarks	No. of cases
Other congenital anomalies	9
Accessory spleen	2
Congenital strabismus	1
Mild mental retardation	1
Micrognathia	2
Retrognathism	1
Umbilical hernia	1
Sacral dimple	1
Birthmarks*	28
Café-au-lait	22*
Non-neoplastic nevus	14*
Hypopigmented macules	1

* Children with multiple birthmarks were assigned to all of their documented birthmark types.

Type of Cancer

Table V shows the distribution of malignant tumors in 72 patients with congenital anomalies and/or birthmarks. Tumors of the central nervous system (CNS) were the most frequent type of cancer diagnosed in patients without an anomaly (n: 494), accounting for 28% of all cancers. Lymphomas were the second most frequent cancer, constituting 23% of all cancers diagnosed in children without abnormalities.

Table V. The Type of Cancer in Patients with Congenital Anomalies and/or Birthmarks

Type of cancer	n (%)
Central nervous system tumors	18 (25)
Lymphomas	12 (16.8)
Wilms tumor	7 (9.8)
Rhabdomyosarcoma	6 (8.4)
Germ cell tumor	6 (8.4)
Malignant bone tumors	5 (6.9)
Neuroblastoma	4 (5.5)
Retinoblastoma	4 (5.5)
Langerhans cell histiocytosis	3 (4.1)
Non rhabdomyosarcoma soft tissue sarcoma	3 (4.1)
Carcinoma	3 (4.1)
Malignant melanoma	1 (1.4)
Total	72 (100)

When patients with only birthmarks were analyzed, the two most frequent types of cancer diagnosed were again CNS tumors (25%) and malignant lymphomas (19.4%).

No particular type of CNS tumor was predominant in any group. The two most frequent types of CNS tumors diagnosed in patients with anomalies (n: 72) were medulloblastoma (33.4%) and astrocytoma (33.4%). In patients without an anomaly (n: 494), medulloblastoma and astrocytoma were again the most frequently diagnosed CNS neoplasms, accounting for 22.9% and 24.3% of the CNS tumors, respectively.

Cancer in Patients with a Defined Syndrome

Nine patients with NF1 developed five different types of tumor: rhabdomyosarcoma (RMS) (n: 3), CNS tumors (n: 3), non-Hodgkin lymphoma (NHL) (n: 1), malignant mesenchymal tumor (n: 1), and malignant peripheral nerve sheath tumor (n: 1). The case with NF2 presented with acoustic neurinoma and ganglioglioma. One case with xeroderma pigmentosum developed epidermoid carcinoma of the skin and the other developed a malignant melanoma. The patient with VHL syndrome had a posterior fossa hemangioblastoma. Two children with IHH typically presented with Wilms tumor.

Age at the Time of Cancer Diagnosis

Table VI shows the distribution of patients according to their age at cancer diagnosis. The distribution of patients according to the time of cancer diagnosis (≤5 years of age versus >5) was not found significantly different between patients with and without an anomaly (chi-

Table VI. The Distribution of Patients According to the Age at Cancer Diagnosis

		Male		Female		Total	
Patients	Age at cancer Dx (years)	No	(%)	No	(%)	No	%
With CMs and/or BMs	≤ 5	15	20.8	13	18.1	28	38.9
	> 5	26	36.1	18	25	44	61.1
	Total	41	56.9	31	43.1	72	100
Without CMs and/or BMs	≤ 5	103	20.9	71	14.4	174	35.2
	> 5	173	35	147	29.8	320	64.8
	Total	276	55.9	218	44.1	494	100

CMs: Congenital malformations. BMs: Birthmarks. Dx: Diagnosis.

square p=0.544). Gender distribution was not found significantly different between these groups (chi- square p=0.864).

Discussion

There is a well-established association of some specific congenital anomalies and dysmorphologic syndromes with childhood cancers[18,21]. In such syndromes like Down syndrome and BWS, the same constitutional genetic defects may lead prenatally to an abnormal clinical phenotype of the individual patient, while postnatally they may lead to abnormal cellular proliferation, predisposing the individual to cancer development[6-11,19-21]. In our series of childhood cancer, the incidence of patients with "childhood cancer syndromes" was 3%, constituting 38.6% of all congenital anomalies. The most frequently defined childhood cancer syndrome was NF1. In a previous study on 1,073 children with cancer, the authors diagnosed a syndrome in 3.9% and suspected the presence of a syndrome in another 3.3%, for a total of 7.2%[21]. They pointed to a possible association and proposed that all children with a malignancy should be examined by a clinical geneticist or a pediatrician skilled in clinical morphology to determine if the patients have a malformation syndrome. Although we could not perform a prospective detailed clinical morphological examination as described by Merks et al.[26], the incidence of patients with a syndrome was 3% in 566 children with cancer. Including IHH cases as a "suspected" syndrome, the frequency of patients with a dysmorphologic syndrome was 23.6% in the anomaly group (n: 72). If only patients with congenital malformations (excluding birthmarks) were included, this figure rises to 38.6%.

Other than the specific syndromes, several studies have shown a relationship between childhood cancer and the presence of major and minor anomalies in children[5,13,15,21,27-29]. Méhes et al.[13] determined a significantly higher prevalence of minor anomalies in children with cancer and their sibs than in the control children: 69% of the patients, 63% of the sibs and 35% of the control subjects had at least one minor anomaly. However, they could not establish any specific association of an individual dysplasia or a pattern of minor anomalies with a given tumor. Merks et al.[21] showed a strikingly high prevalence of phenotypic abnormalities, such as supernumerary nipples, café-au-lait spots, abnormal palmar flexion creases, and leg length asymmetry in 1,073 children with cancer. In our study, a major or minor anomaly excluding birthmarks was documented in 7.8% of cases. If birthmarks are also included, this incidence rises to 12.7%. We could not find any reports on the incidence of congenital malformations in children with cancer from Turkey with which to compare our results. However, some studies from different regions of Turkey had previously reported on the frequency of anomalies in children without cancer (Table VII). Say et al.[30] and Yeşilipek et al.[31] reported a prevalence of 2.1% and 2.3% in live births, respectively. Tunçbilek et al.[32] reported 3.7% incidence of congenital malformations in 21,907 Turkish babies. Himmetoğlu et al.[33] reported an overall congenital anomaly incidence of 1.1% in newborns. Yücesan et al.[34] reported a 6.1% prevalence in school children. Considering the different study cohorts and methodological differences, our results can not be directly compared with these previously reported findings. However, the incidence of minor and major malformations in our patients with childhood cancer suggests a higher frequency of congenital malformations in children with cancer.

Recently, Johnson et al.[15] reported an association between childhood cancer and birthmarks in the Collaborative Perinatal Project (CPP). They found birthmarks to be in excess in

Table VII. The Frequency of Congenital Malformations in Turkish Pediatric Series

	Patients (n)	Prevalence of CMs	Incidence of CMs	Year	Reference (no)
Current study	566 children with cancer		7.8%	2007	–
Say et al.	10,000 live births	2.1%		1971	(30)
Yeşilipek et al.	25,650 live births	2.3%		1989	(31)
Yücesan et al.	19,750 school children	6.1%		1993	(34)
Himmetoğlu et al.	9,160 neonates		1.1%	1996	(33)
Tunçbilek et al.	21,907 babies		3.7%	1999	(32)

CMs: Congenital malformations.

children who received a diagnosis of cancer (15% of cancer cases and 5% of non-cases), with strawberry hemangiomas and port-wine stains being the most common in both groups. This study showed that having a documented definite or suspected birthmark was associated with a significantly increased hazard of cancer (hazard ratio [HR]: 3.19; 95% confidence interval [CI]: 1.43-7.12). However, even this large prospective cohort study failed to show any specific childhood malignancy notably affected by birthmarks. In our study, we analyzed birthmarks that were not part of a spectrum for a specific syndrome. Twenty-eight out of 566 cancer patients (4.9%) had birthmarks. This figure was lower than the reported incidence. A study performed in a dermatology clinic from our region reported a higher incidence of birthmarks (19.2%)[35]. This result suggested that some birthmarks had been overlooked or had not been noted in the records. We can conclude neither on the incidence of birthmarks in children with cancer nor on the association of birthmarks with childhood cancer due to the small number of patients and retrospective data.

All cases assigned to the "syndrome" group had typical tumors associated with these disorders[18,21]. Patients with NF are at risk for malignancies, especially malignant peripheral nerve sheath tumors, sarcomas, brain tumors, childhood leukemia, and other cancers[22-25]. In this patient group, nine children with NF1 developed some neurogenic and non-neurogenic tumors, all of which have been reported to occur frequently in these patients[18,21-25]. The other children with well-defined "cancer-prone syndromes" in this study also had typical cancers associated with the particular syndrome[18,21]. The child with NF2 presented with acoustic neurinoma and ganglioglioma. One child with xeroderma pigmentosum developed epidermoid carcinoma and basal cell carcinoma of the skin and the other developed a malignant melanoma. The patient with VHL syndrome had a posterior fossa hemangioblastoma, and two cases with IHH presented with Wilms tumor. Cancer occurrence had been reported at a younger age in patients with a specific malformation syndrome[21]. We were not able to show any significant difference between the age at cancer diagnosis (≤5 years versus >5 years) and congenital malformations. The number of patients was too low to show such a specific relation.

In several studies, children with congenital abnormalities were found to have a significantly higher risk of developing some type of cancer, including leukemia, tumors of the CNS, tumors of the sympathetic nervous system, and soft tissue sarcomas[5,6,27-29]. Narod et al.[27] reported a higher rate of congenital anomalies among the records of 20,304 children with solid tumors, when compared with general population rates. They showed higher rates of anomalies in patients with Wilms tumor, Ewing sarcoma, hepatoblastoma, and gonadal and germ cell tumors. Agha et al.[29] reported that leukemia (25.2%) and CNS tumors (20.5%) were the most frequent cancers diagnosed in children with and without abnormalities. One of the major limitations of our study was the lack of leukemia patients, which is the most common childhood cancer (26%) in our institution. In our study, the most common cancer types were CNS tumors and lymphomas both in patients with and without an anomaly and/or birthmark. This figure probably reflects the general incidence rates for childhood cancer in our center. The second and third most common childhood malignant diseases were CNS tumors (21%) and lymphomas (14%), respectively, in our institution[36]. Another finding in Agha et al.'s[29] analyses was the presence of seven cases of medulloblastoma in the group of CNS tumors diagnosed among children with abnormalities compared with no such cases diagnosed in children without abnormalities. In our series, the incidence of medulloblastoma was almost equal to that of astrocytomas in both groups. The number of patients was too low to show any significant association between a particular anomaly and a specific cancer type. Even studies in large cohorts were not able to examine the association between specific cancer types and specific abnormalities due to the rarity of cancer in children and the wide diversity of congenital anomalies[29].

A sociodemographic factor that might contribute to the recessive anomalies is consanguinity between parents. The rate of consanguineous marriages in our study group was high (12.6%), although remarkably lower than the reported rate (20-25%) in Turkey[37]. However, we could not show any difference in this incidence between patients with and without anomaly. The history of cancer in the family was positive in 31% of the patients, with no significant

difference between groups. Only two families fulfilled the clinical criteria for the Li-Fraumeni syndrome. Although the number of particular tumors was too low for any subgroup analysis, this finding is also noteworthy and deserves further investigation in large series.

To our knowledge, this is the first report from Turkey searching for the incidence of congenital malformations and birthmarks in children with cancer. However, there were some limitations to this study. It was a retrospective analysis in a small number of patients without a control group. Only available data on the presence of congenital anomalies either with physical examination and/or radiological examinations, which were not particularly directed to phenotypic abnormalities using detailed definitions, could be evaluated. Leukemia, the most common cancer of childhood, could not be included.

However, the high incidence of congenital anomalies and childhood cancer syndromes even in this retrospective analysis may stimulate future large cohort studies in our country. Because congenital anomalies and childhood cancer are both uncommon events, only prospective detailed monitoring of large cohorts of childhood cancer patients will show the true nature of these associations. This could be a very fruitful area of research since we have a young population and the incidence of congenital malformations might be higher than in the developed countries owing to the high rate of consanguineous marriages in our country[37]. Cumulating data on the association of congenital malformations and cancer can improve our understanding of the normal development and the pathophysiology of cancer. The information on this critical issue can also help us to identify early the children and their family members at risk for cancer. Tumor registries such as the Turkish Pediatric Oncology Group (TPOG) and the Turkish Pediatric Hematology Society (TPHD) are valuable resources in this respect (38,39). Collaboration of clinical geneticists and pediatric oncologists could definitely improve our knowledge on the association of congenital malformations and cancer.

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