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Association of Childhood Rhabdomyosarcoma With Neurofibromatosis Type I and Birth Defects

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Rhabdomyosarcoma (RMS) is an uncommon malignant soft tissue sarcoma whose cause is largely unknown. Reported risk factors include genetic alterations (e.g., p53 mutations, a defective gene at 11p15.5, or specific chromosomal translocation of t(2;13)), and parents' use of drugs around the time of conception. We present results from a national, case-control study of 249 RMS cases (170 males and 79 females) and 302 controls (196 males and 106 females). The cases, aged 0–20 years at diagnosis, were identified via the Intergroup RMS Study-III during 1982–1988. Controls were selected by random digit telephone dialing. As a supplement to the original study, information on genetic diseases and birth defects (BD) was collected from the subjects' parents by telephone interview. Fifty-six (22.5%) cases and 55 (18.2%) controls were reported to have genetic diseases or BD (odds ratio [OR] = 1.30, 95% confidence interval [CI] = 0.85–2.02, P = .21). The case group had a significantly higher frequency of neurofibromatosis type I (NF1) than did the control group, i.e., five cases (2.0%) had NF1 vs. zero controls (P = .02). The case group also had a higher frequency of major BDs than did the control group (6.0% vs. 2.6%, OR = 2.36, 95% CI = 0.92–6.52, P = .05). However, this excess was only observed in males (7.6% vs. 2.6%, OR = 3.16, 95% CI = 1.02–10.41, P = .02). Among the 15 cases having both RMS and major BDs, six (40.0%) had

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both conditions in the same regional anatomic site: Two (13.3%) had both in the extremities, two (13.3%) in the genitourinary system, and two in the head and neck. These findings suggest that common genetic mechanisms or in utero exposures may be involved in the development of many childhood tumors and congenital abnormalities.

Key words: rhabdomyosarcoma, neurofibromatosis, congenital abnormalities, genetic epidemiology

INTRODUCTION

In children, rhabdomyosarcoma (RMS) is the most common type of soft tissue sarcoma and can occur in many sites of the body [Donaldson, 1987]. Among children aged 0–14 years, the annual incidence of RMS in the United States is estimated to be 4.4/1,000,000 in whites and 1.3/1,000,000 in blacks [Young et al., 1986]. An excess risk of RMS in males has been reported [Donaldson, 1987; Young et al., 1986; Grufferman et al., 1984]. Even within the childhood group, there are two peaks in RMS incidence: One occurs soon after birth and the other at puberty. The latter peak has been postulated to be hormonally related [dos Santos Silva and Swerdlow, 1993].

Although little is known about the cause(s) of RMS, several factors including genetic alterations and environmental exposures have been reported to be associated with its occurrence. A higher frequency of congenital abnormalities has been seen in RMS patients [Ruymann et al, 1988; Hartley et al., 1988a,b], and the constellation of malignancies termed Li-Fraumeni syndrome often involves RMS [Hartley et al., 1991; Birch et al., 1984; Li and Fraumeni, 1982]. Several chromosomal aberrations have been indicated in specific subtypes of RMS, i.e., a defective gene in chromosome region 11p15.5 and embryonal RMS and translocations involving chromosome 13 and alveolar RMS [Scrable et al., 1989; Loh et al., 1992; Douglass et al., 1991]. A recent study [Grufferman et al., 1993] reports a two- to fivefold increased risk of RMS in children whose parents used marijuana and cocaine during the year before their birth.

An observed association of RMS, neurofibromatosis type I (NF1) and birth defects (BD) has been reported in the literature. NF1, one of the most common autosomal dominant genetic diseases, has been found much more frequently than expected among children with RMS, and vice versa [Shearer et al., 1994; Matsui et al., 1993; Hartley et al., 1990; Cohen and Rothner, 1989; Ruymann et al., 1988; Hartley et al., 1988a,b; Bader, 1987; Blatt et al., 1986; Schneider et al., 1986; Warrier et al., 1985; Hope and Mulvihill, 1981]. Among children with RMS, the prevalence of NF1 has been reported to be between 1.4% and 6.0%, while the prevalence of NF1 in the general population is approximately 0.03–0.4% at birth [Crowe et al., 1956; McKeen et al., 1978]. Heyn et al. [1993] recently reported a correlation between second malignancies in children treated for RMS and a positive family history of NF1 or cancer. Of the 1,774 RMS patients she followed, 24 developed second malignancies, and 12 of those 24 children (50%) had a known family history of one or more relatives having another type of cancer or NF1. Birch et al. [1990] found an over 60% excess of cancer occurrence in first-degree relatives of children with soft tissue sarcoma compared to the general population. The mean ages at diagnosis were 44.7 and 15.2 years for parents and siblings, respectively. Hartley et al. [1988 a,b] found an

excess of congenital malformations in children with soft tissue sarcoma and an excess of malignant and borderline malignant tumors in the mothers of these children. Ruymann et al. [1988], reported that among 115 autopsied RMS cases, 37 (32%) had congenital anomalies. These anomalies most frequently involved the gastrointestinal (12% of the autopsied cases), genitourinary (10%), and central nervous (8%) systems. We present our results from a national case-control study in which cases were identified through the Intergroup RMS study (IRS) of the Childrens' Cancer Group and the Pediatric Oncology Group. Our goal is to provide evidence for the hypothesis that genetic predisposition may underlie the development of certain congenital abnormalities and malignant tumors by confirming the association of RMS with NF1 and major congenital abnormalities.

DATA AND METHODS

Patients with rhabdomyosarcoma, aged 0–20 years at diagnosis, were identified through the IRS-III during April 1982 to July 1988 [Ruymann and Grufferman, 1991; Grufferman et al., 1984; Maurer et al., 1991]. Cases were from 69 hospitals in 42 states and the District of Columbia; all cases underwent central pathologic review to confirm diagnoses. Controls were selected by random digit telephone dialing. Each case's area code and first five digits of the telephone number were used with two randomly selected terminal digits to search for a control who matched the case on the basis of race, sex, and age. A more detailed description of case and control selection methods has been published elsewhere [Grufferman et al., 1993]. In total 361 matched pairs were eligible for the study. A supplement research component was added to the original study design during the 2nd year of data collection. Information on genetic disease and BD was collected from subjects' parents by telephone interview using a structured questionnaire. All reported BD were classified blindly as major or minor BD [Jones, 1988; Stevenson and Hall, 1993; Khoury et al., 1993]. Overall, complete interview including the supplemental information was available for 249 cases (170 males, 79 females) and 302 controls (196 males, 106 females).

The differential participation rates in the telephone interview on genetic diseases and BD between cases (69.0%) and controls (83.7%) reflects the delay in finding appropriate matched control subjects via random digit telephone dialing. As is the usual situation in a case-control study, cases were identified and interviewed first and then controls for the cases were identified. As a result, proportionately more cases than controls had already finished their telephone interviews at the time the supplemental component began. To examine whether any potential selection bias was presented in the subset of subjects completing the supplemental component of the interview, subjects with information on genetic disease and BD (249 cases and 302 controls) were compared to the total number of subjects (361 case-control pairs) for mean age at diagnosis, gender, and the anatomic site and histopathological type of RMS. No substantial differences were found between the two groups.

Chi-square tests were performed, using Epi-Info (version 5.00), for all of the comparisons between the case and control groups when the number of subjects in each group was adequate, and two-tailed Fisher's Exact tests were applied when the expected number of subjects in any group was less than five.

TABLE I. Occurrence Of Congenital Anomalies in Rhabdomyosarcoma Cases And Controls

	Cases (%)	Controls (%)	Odds ratio (95% CI)	*P* value
No Anomalies	193 (77.5)	247 (81.8)		—
All anomalies	56 (22.5)	55 (18.2)	1.3 (0.85–2.02)	0.21[a]
Genetic defects				
NF1	5 (2.0)	0	—	0.02[b]
Hemophilia	0	1 (0.3)	—	0.55[b]
Major malformations	15 (6.0)	8 (2.6)	2.36 (0.92–6.18)	0.05[a]
Minor malformations	36 (14.5)	46 (15.2)	0.94 (0.57–1.55)	0.89[a]
Total	249 (100)	302 (100)	—	—

[a]By chi-square test.
[b]By two-tailed Fisher's Exact test.

RESULTS

The frequencies of congenital anomalies in the case and control groups are presented in Table I. Overall, 56 (22.5%) cases and 55 (18.2%) controls were reported to have congenital anomalies; a non-significant difference ($P = .21$). However, when the congenital anomalies were grouped into genetic defects and major and minor congenital malformations, the case group had a significantly higher prevalence of NF1 ($P = .02$) and major malformations ($P = .05$) than did the control group. The excess of major BD in cases was observed in males (7.6% vs. 2.6%, OR = 3.16, 95% CI: 1.02–10.41, $P = .02$) but not in females (2 cases and 3 controls, 2.5% vs. 2.8%, respectively), which might be due to chance and the small sample size.

The observed prevalence of minor congenital abnormalities in each group, 14.5% in cases and 15.2% in controls, is comparable with the 15% rate reported in the general population [Stevenson and Hall, 1993; Jones, 1988; Marden et al., 1964].

Age at diagnosis, histopathologic type, and primary site of the RMS in relation to the BDs were examined for the cases who had both RMS and NF1 and for those who had both RMS and a major BD. There are four major histopathologic groupings of RMS cases: embryonal (67.9%), alveolar (22.1%), undifferentiated (5.2%), and other (4.8%). All five cases who had both RMS and NF1 (Table II) had embryonal RMS, and all were diagnosed before the age of 3 years with a mean age of 1.3 years.

Among the 15 cases who had both RMS and one or more major BD (Table III), six (40.0%) had both in the same or adjacent anatomic sites: two had both in the extremities; two were in the genitourinary system; and two were in the head and neck. There were two cases, patients 8 and 9, who had clubfoot at birth and later

TABLE II. Characteristics of Cases With Rhabdomyosarcoma and Neurofibromatosis Type 1

Case	Sex	Age (in years) at diagnosis	RMS site	Pathologic type
1	M	2.5	Mid-ear	Embryonal
2	M	2.7	Abdominal wall	Embryonal
3	M	0.5	Bladder	Embryonal
4	M	0.1	Prostate	Embryonal
5	F	0.9	Vagina	Embryonal

TABLE III. Characteristics of Cases With RMS and Major BD

Case	Sex	Age (years) at diagnosis	Pathologic group	Primary RMS site	Major BD
6	M	12.1	Embryonal	Leg	Severely malformed feet, walked on ankles
7	M	10.5	Alveolar	Foot	Clubfoot
8	M	3.8	Alveolar	Arm	Clubfoot
9	M	15.8	Embryonal	Arm	Clubfeet
10	F	1.9	Embryonal	Uterus	Double vagina & cervix, cystic ovary & kidney, birth marks
11	M	2.2	Embryonal	Prostate	Imperforate anus, hypospadias, small kidney, urethra bent
12	M	9.1	Embryonal	Testis	Clubfeet
13	M	16.2	Embryonal	Testis	Cleft palate
14	M	3.7	Alveolar	Nasal cavity	Cleft palate
15	M	10.7	Embryonal	Nasopharynx	Tracho-esophageal fistula
16	M	18.7	Alveolar	Nasopharynx	Clubfeet
17	M	4.4	Embryonal	Parameningeal	Pyloric stenosis
18	M	7.3	Embryonal	Mid-ear	Hypospadias
19	M	8.9	Embryonal	Unknown	Hypospadias, heart murmur
20	F	2.9	Alveolar	Arm	Dislocated hip

developed RMS in their arms. It was worth noting that two cases, cases 10 and 11, who were diagnosed with RMS at age 1 and age 2, respectively, had severe BD in the anatomic sites where the RMS occurred. There were six cases (40.0%) with RMS and BD in different sites, and one case (6.7%) with hypospadias and an unknown site for RMS.

Mean age at diagnosis of these 15 cases in Table III was 8.4 years. Pathologic diagnoses were also examined for these 15 cases. Ten of them (66.7%) were embryonal and five (33.3%) were alveolar. All four cases with genitourinary RMS were embryonal.

DISCUSSION

Our results demonstrate an association between RMS and NF1, and between RMS and major congenital abnormalities. These findings are consistent with those from previous studies.

Matsui et al. [1993] assessed the frequency of NF1 in over 26,000 childhood cancer patients (< 15 years old) in the Japanese Children's Cancer Registry. The authors observed that 1.4% (6/440) of children with RMS also had NF1, which is very similar to our study results. We found a prevalence of 2.0% (5/249) NF1 in our RMS case group and none (0/302) in our control group.

McKeen et al. [1978] reviewed a group of 84 consecutive cases with RMS and detected five with NF1 (6%). This seemingly high rate of NF1 among RMS patients, compared to the results of Matsui et al. [1993] and our study, may be due to differences in the method of case selection. Cases involved in the study of McKeen et al.

were hospital based and were from the Children's Hospital of Philadelphia and the National Cancer Institute, whereas cases in the study of Matsui et al. [1993] were from a population registry in Japan. Cases in our study were from 69 hospitals in 42 states and the District of Columbia; they represent over 80–85% of all childhood RMS cases diagnosed in the United States [Grufferman et al., 1984, 1993].

All of the cases who had NF1 were very young at their RMS diagnosis, and 80% (4/5) of them were male. These findings were consistent with the results reported by Hartley et al. [1988a] and Warrier et al. [1985]. Cumulating evidence from the literature of the RMS-NF1 association supports the hypothesis that the NF1 mutant gene may be involved with at least a subgroup of cases for their RMS development [Matsui et al., 1993].

Congenital anomalies are often divided into major and minor defects even though there is no clear division between major and minor BD. Anomalies which pose medical and social consequences are considered major [Stevenson and Hall, 1993; Czeizel, 1993]. Major malformations occur in 2–4% of live-born infants [Stevenson and Hall, 1993]. Minor anomalies are more common, occurring in approximately 15% of newborns [Jones, 1988; Marden et al., 1964]. However, in babies with two or more minor defects (1% of all newborns), there is a five- to 30-fold increased risk of having one or more major malformations [Jones, 1988; Cohen and Michael, 1982; Nyhan, 1976; Marden et al., 1964]. Identifying minor anomalies often requires particular attention, especially for certain malformations of the extremities which may be at the borderline between major and minor defects [Bossers, 1980].

In a survey of children registered with IRS I and IRS II, Ruymann et al. [1988] examined 115 eligible RMS cases for whom an autopsy report was available. They found one case (0.9%) with NF1 and 37 cases (32.2%) that had at least one congenital malformation. Fourteen of the 45 identified anomalies were major and 31 were minor. Based on information given in their Tables II–V, approximately 9% of their total cases had major defects and over 20% had minor defects. One of the reasons for the higher prevalence of congenital anomalies observed in the study of Ruymann et al. than that reported here, especially for minor malformations, is that they assessed malformations from autopsy information. This information was not available for our cases. Thus, they identified defects which could not be detected by external examination, e.g., capillary telangiectasia of the right parietal white matter, multiple renal veins, and small unilateral ovarian cyst. Another recent study [Hartley et al., 1994], in which a higher rate of malformations was found in siblings of female children with soft tissue sarcoma, was based on 118 children who were diagnosed under the age of 15 years and registered with the Manchester Children's Tumor Registry during 1954–1991.

We believe the observed concordance of the anatomic location of RMS and major BD is most interesting. Forty percent of the cases with both RMS and a major BD had both in the same anatomic sites, and an additional 13.3% had both in the same organ systems which were derived from the same developmental field in the embryo, e.g., the limb bud [Opitz and Lewin, 1987]. This concordance may indicate common causes underlying both RMS and major BD. As an hypothesis, the same genetic alteration or early in utero exposure could affect normal embryo development causing structural defects, and predispose the individual to embryonal malignancies during

early life. The specificity of genetic alteration, e.g., the homeobox genes [Cillo et al., 1992], and the timing and the location of the exposure, may explain the heterogeneity of the cancer-malformation association and the variety of the structural defects in the same cancer groups. In our study, cleft palate, pyloric stenosis, hypospadias, double vagina, and clubfeet were all observed in cases who later developed genitourinary embryonal RMS.

In conclusion, although the association of RMS with NF1 and BD has been reported previously in case reports, case series, and autopsy studies, this is the first conformation of this association from a large, national, case-control study. We found a significant excess of NF1 and of major congenital abnormalities in the cases when compared to the controls, but there was no difference in minor birth defects between the two groups.

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