Congenital Fibrosarcoma and History of Prenatal Exposure to Petroleum Derivatives

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KEY WORDS

environmental health, childhood cancer, prevention, fibrosarcoma, petroleum derivatives

ABBREVIATIONS

CFS—congenital fibrosarcoma

IARC—International Agency for Research on Cancer

PEH—Pediatric Environmental History

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abstract

Congenital fibrosarcoma (CFS) is a rare fibrous tissue malignancy that usually presents in the first few years of life. It is unique among human sarcomas in that it has an excellent prognosis. We describe a temporal clustering of a number of cases of CFS and investigate the possible associated prenatal risk factors. The Pediatric Environmental History, a questionnaire developed in our clinic that is instrumental in determining environmental risk factors for tumor-related disease, was essential in documenting the presence or absence of risk factors considered as human carcinogens. We found a history of exposure to petroleum products in four cases of CFS that occurred at a greater than expected rate in a short time frame—an apparent cancer cluster. We call attention to the possibility that exposure to petroleum products raises the risk of developing CFS. While future studies should focus on systematic investigation of CFS and its underlying mechanisms, this report suggests the need for proactive measures to avoid exposure to solvents and petroleum products during pregnancy. *Pediatrics* 2012;130:e1019–e1025

Congenital fibrosarcomas (CFS) are soft-tissue sarcomas diagnosed at or soon after birth¹ and represent ~5% to 10% of all sarcomas occurring in infants <1 year.^{2–5} With an estimated incidence of 3.7/million live births, CFS presents typically a ETV6-NTRK3 gene fusion as a result of a t(12;15)(p13;q25) translocation.⁶ The chromosomal translocation may arise as a result of unfaithful repair of spontaneous DNA double-strand breaks, most probably induced by oxidative stress, radiation, or genotoxic chemicals.⁷ Although no chemical carcinogen has been identified to date, several risk factors have been associated with soft-tissue sarcomas in children: congenital anomalies, genetic conditions (Li-Fraumeni syndrome and neurofibromatosis type 1), low socioeconomic status, ionizing radiation (in utero), and parental use of marijuana and cocaine during the pregnancy.⁸ The Integrated Risk Information System is a US Environmental Protection Agency database of potential health effects from environmental substances focusing on hazard identification and dose-response and carcinogenicity assessment. With the use of this system, we identified 16 substances associated with fibrosarcoma (Table 1). Only one, dibenz[a,h]anthracene, is likely a human carcinogen. The identified risk factors for infantile fibrosarcoma are unknown. The Pediatric Environmental History (PEH) questionnaire is a tool that allows for the registration of environmental risk factors related to tumor disease (Table 2).⁹ We report a suspected cluster of 4 CFS cases and illustrate the potential utility of PEH in identifying risk factors for CFS.

METHODS

Patients and Study Design

Medio Ambiente y Cáncer Pediátrico—Environment and Pediatric Cancer Group is a project for the compilation

of PEH in patients newly diagnosed with cancer since 2003.^{9–12} Centralized care in pediatric oncology referral units in Spain facilitated the access to the medical records in the La Fe University/Children's Hospital, the Valencia University Hospital, and the General University Hospital of Alicante, which register 100% of the children diagnosed with cancer in the Valencian Community (population 4.5 million in 2004). Three cases of CFS were verified, raising the suspicion that there is an excess of cases for that short time period. The presence of these cases led to a careful review of the hospital registries and data from the Valencian Community back to 2001 of all the children diagnosed with fibrosarcoma <5 years of age.

We studied a suspected cluster of 4 cases of CFS in the greater Valencia region in Spain (Fig 1). All of the CFS cases were diagnosed between 2001 and 2004 and were registered in the Regional Registry of Tumors and in the database of hospitals collaborating in this survey (reaching >99% of area cases).

The first case of CFS was diagnosed in 2001 in Castellon, 2 cases were diagnosed in 2004 in Valencia, and 1 was diagnosed in the nearby Xativa. All the cases corresponded to the anatomopathological diagnosis of CFS in newborns (located in the abdominal, facial, forearm, and thigh regions) and had the t(12;15)(p13;q25) translocation, typical of CFS.

Expected cases for live children were calculated by using the Autonomic Community of Valencia as reference population.¹³ The incidence of CFS is estimated to be 3.7 cases/million in newborns, up to 8 cases/million in children <1 year of age and 2 cases/million in children <5 years of age.^{6,12} To evaluate the risk, we used the standardized incidence ratio with a 95% confidence interval.^{14,15} The *Scan* statistic test¹⁶ was used for identifying

temporal, spatial, and spatiotemporal clusters.

Exposure Data: Pediatric Environmental History

The PEH tool comprises a series of concise and basic questions formulated to identify environmental exposures of concern and to document human carcinogens characterized by the International Agency for Research on Cancer (IARC) and by the US National Toxicology Program.^{17,18} The PEH questionnaire is applied to all patients with cancer and all pediatric consultations at the Pediatric Environmental Health Specialty Unit. The interview is a structured or semistructured process, a standardized form is used, and the questions are either open ended or multiple choice. The interview was conducted, in person, by 1 pediatrician with one or both parents present. Informed consents were obtained from the parents participating.

Chemical Carcinogenesis Research Information System, a database sponsored by the National Cancer Institute containing data on carcinogens, mutagens, and tumor promoters, was reviewed, documenting registered chemical substances associated with fibrosarcoma. The La Fe University/Children's Hospital ethics committee and the institutional review boards approved the study.

Case Reports

Patient 1

A male patient born at 37 weeks of pregnancy, 3500 g. Retroperitoneal neonatal fibrosarcoma was detected at 34 weeks of pregnancy. Patient did not show any malformations at birth and died at 48 hours because of surgical complications. There was no family history of cancer of first- and second-degree relatives. The mother was primigravida, a nonsmoker and

TABLE 1 Integrated Risk Information System Database Focusing on Hazard Identification and Dose-Response and Carcinogenicity Assessment in the Development of Fibrosarcoma

Chemical Substance Name	Human Evidence	EPA Classification Carcinogenesis	IARC ^a
Aniline	Chemical dye industry (Britain)	B2: probable human carcinogen	3
Dibenz[a,h]anthracene	No direct exposure, but included in coal tar, soot, cigarette smoke	B2: probable human carcinogen	2A
Aldicarb	No evidence in humans	D: not classifiable as to human carcinogenicity	3
Glycidaldehyde	None, only animal data	B2: probable human carcinogen	2B
Naphthalene	No data available or inadequate	C: possible human carcinogen (1986), cannot be determined (1996)	2B
Silver	No evidence in humans	D: not classifiable as to human carcinogenicity	Not classified
Benza[a]anthracene	No direct exposure, but included in coal tar, soot, cigarette smoke	B2: probable human carcinogen	2B
Refractory ceramic fibers	None, sufficient animal data	B2: probable human carcinogen	2B
1,2-Dibromoethane	Data from production facilities yields inconclusive results, and data are inadequate	Likely to be carcinogenic to humans	Not classified
Isophorone	No data on humans, limited in animals	C: possible human carcinogen	Not classified
Propylene oxide	Inadequate, German production plants	B2: probable human carcinogen	2B
Manganese	No data on humans, inadequate in animals	D: not classifiable as to human carcinogenicity	Not classified
Boron and compounds	Data not available, animal data inadequate	Unsure classification	Not classified
Azobenzene	None, sufficient data in animal	B2: probable human carcinogen	3
Toluene	Limited or no evidence suggest carcinogenic effects, animal data no evidence either (2 y)	Inadequate information to classify	3
Oryzalin	No human studies, limited study in animals	C: possible human carcinogen	Not classified

EPA, Environmental Protection Agency.

^a IARC classification: group 1, carcinogenic to humans; group 2A, probably carcinogenic to humans; group 2B, possibly carcinogenic to humans; group 3, unclassifiable as to carcinogenicity in humans; group 4, probably not carcinogenic to humans.

nondrinker, worked in a family-owned gas station during pregnancy, being exposed to petroleum derivatives by inhalation. The mother used Bondex (nafta, 3-butoxy-2-propanol) polish in the home during the second trimester of pregnancy. She worked as a gas-station attendant and at the office for

40 hours/week without using any protection. A chest radiograph was performed on day 11 of pregnancy because of an anxiety crisis.

Patient 2

A female patient born at 40 weeks of pregnancy, 3300 g. Mother experienced

a diet-controlled gestational diabetes. On delivery, patient was found to have a fibrosarcoma in the right thigh and no malformations. There was no family history of cancer of first- and second-degree relatives. The patient was the first pregnancy for the mother. Both parents smoked during the pregnancy

TABLE 2 Main Sections of the Pediatric Environmental History^a

Family history and associated constitutional symptoms

Pedigree of at least 3 generations for:

- History of cancer in the family tree
- Genetic and constitutional factors associated with childhood cancers
- Chronic, rare and family diseases
- Causes of death

Detailed description of sources of exposure during pregnancy

Maternal grandmother's (maternal egg formation) work during pregnancy and drugs in pregnancy

Maternal grandfather's work during pregnancy

Environmental exposures (preconceptional, conceptional, pregnancy, postnatal)

The data collection is distributed in the following sections:

- General (affiliation and identification, and socioeconomic data), housing (before, during pregnancy, and postnatal), tobacco (before, during pregnancy, and postnatal), external environment (neighborhood, daycare, school), lifestyle during pregnancy and postnatal care, perceptions (before, during pregnancy, and postnatal)
- Nutrition during pregnancy and exercise
- Obstetric history (drugs, diseases, etc)
- Radiologic history of the parents
- Work history (both parents)
- Background of the child (birth, neonatal, radiation history, diseases, vaccines, treatments, etc)
- Breastfeeding
- Nutrition of the child, exercise, and lifestyle

Type of tumor (tumor data, diagnosis, treatment, and evolution)

FIGURE 1

Spatiotemporal fibrosarcoma distribution in Valencia Region. Temporal distribution of fibrosarcomas.

and did not consume alcohol. Mother was not exposed to ionizing radiation. The father, a mechanic, was exposed to substances used in cleaning industrial and automobile compressors. The mother worked as a gas-station attendant without using any protection for 40 hours/week for 2 years before conception and during the pregnancy and was exposed to gasoline derivatives via inhalation and dermal pathways.

Patient 3

A female patient, born at 38 weeks at 3560 g. Patient did not show any malformations at birth. There was no known family history of cancer in the first- and second-degree relatives. Patient was the second pregnancy of her mother. Both parents smoked throughout the duration of pregnancy and had no significant exposure to occupational carcinogens, ionizing radiation, alcohol, and medicinal or illegal

drugs. During pregnancy, the family lived in a home located ~10 m from a gas station, thus exposing the mother to possible inhalation of gasoline-related fumes (all of the windows of the home were open for 4 hours/day).

Patient 4

A female patient, born at 39 weeks weighing 3260 g. The mother presented with hypertension, which was treated during pregnancy. There was an observation of a CFS in the patient's forearm and no malformations at birth. There was no family history of cancer observed in the first and second generations. The patient was the second pregnancy of her mother. Both parents were identified as smokers, and there was no consumption of alcohol or exposure to ionizing radiation. The mother performed certain tasks involving exposure to paint while pregnant. In addition, the couple bought

a set of new furniture during that time. The father was employed in a family-owned company that manufactures chromium- and nickel-related products and uses gasoline and other petroleum-derived solvents. The father may have introduced these contaminants into the home by returning home wearing contaminated clothing and shoes. All cases are summarized in Table 3.

RESULTS

Statistical Analysis

The population in the Valencia region was 653 158 children <15 years (14.38% of the total population) in 2004 (Table 4). Table 4 illustrates the standardized incidence ratio values for each year of study. The 2004 referral population expected at birth stands out with a value of 16.56. By using SatScan software (<http://www.satscan.org>) we obtained the Scan statistic.

TABLE 3 Data From Pediatric Environmental History

Patient	1	2	3	4
Birth	April 2004	April 2001	January 2004	April 2004
Gender	Male	Female	Female	Female
Location	Abdominal	Thigh	Facial	Forearm
Diagnostic date	Prenatal	At birth	Prenatal	At birth
City (province)	Xativa (Valencia)	Castellón (Castellón)	Valencia (Valencia)	Valencia (Valencia)
Associated malformations	No	No	No	No
Familial history/hereditary cancer syndrome	No	No	No	No
Diseases (mother)	Allergies	Diabetes (gestational)	None	Hypertension
Diseases (father)	None	None	None	None
Tobacco in pregnancy				
Mother (cigarettes/d)	Mother: no	Mother: 5	Mother: 7	Mother: 1–3
Father (cigarettes/d)	Father: 20	Father: 20	Father: 10	Father: 30
Passive	Significant exposure	Significant exposure	Significant exposure	Significant exposure
Recreational drugs	No	No	No	No
Medical ionizing radiation in utero	Yes	No	No	No
Mother's occupation	Gas station worker	Gas station worker	Office	Housewife
Father's occupation	Box cutter cardboard factory	Mechanic	Office	Chromium and nickel plating
Pesticides at home	Yes	No	No	No
Mother's educational level	College	Primary school	College	Primary school
Father's education level	Secondary	Primary school	Secondary	Primary school
Net income/month (€)	2500–3500	1500–2000	2000–2500	1500–2000
Exposure to gas derivatives	Yes, significant	Yes, significant	Yes, significant	Yes, significant
Indoor solvents	Yes	No	No	Yes
Home near an industrial site or major highways	No	No	Yes (gas station)	No

With monthly disaggregation we identified a temporal cluster between January and April 2004 (P -value = .05), and with year disaggregation the highest likelihood cluster is the 2004 year with a P value of .276. There is no significant spatial cluster. Finally, we identified a spatiotemporal cluster with 50 municipalities (shading in Fig 1) during January through April 2004 (P -value = .10).

Review of the Chemical Carcinogenesis Research Information System Database

Sixty-two different chemical substances are known to cause fibrosarcoma in animals under experimental conditions. None of the substances have

been tested for intrauterine exposures. Only 3 have been identified to produce fibrosarcoma when inhaled: chrysotile asbestos, ethylene dibromide, and nickel subsulfide.

Clinical Findings

Prenatal exposure to gas solvents and its derivatives was present in 3 CSF cases associated with occupational exposure at gas stations and the fourth with indirect exposure at home. Additionally, all cases were exposed to carcinogens from tobacco smoke. In Spain, 50% of children live with a daily smoker.¹⁹ It is therefore difficult to attribute the effect of smoke exposure. It is also difficult to attribute the importance of ionizing radiation on the

development of fibrosarcoma, because, during the period of blastogenesis, the cells have a great pluripotency to repair themselves.

DISCUSSION

We found a history of exposure to petroleum derivatives in 4 cases of CFS. By using the PEH, a clinical tool to develop a description of suspected cancer cluster, we identified a CFS cluster, although it is not sufficient to meet the Bradford-Hill causal criteria. Previous examples of unusual cancer clusters that led to the identification of a previously unrecognized human carcinogen include scrotal cancer in chimney sweeps exposed to soot, osteosarcoma

TABLE 4 Population and Standardized Incidence Ratio in Valencia Region

Year	P _b	P ₁	P ₅	P ₁₅	0	S _b	S ₁	S ₅	SIR _b (CI 95%)	SIR ₁ (CI 95%)	SIR ₅ (CI 95%)
2001	0.04	0.06	0.18	0.60	1	0.16	0.28	0.36	6.39 (0.08–35.56)	3.53 (0.05–19.63)	2.82 (0.04–15.67)
2002	0.04	0.06	0.19	0.61	0	0.16	0.30	0.38	0.00 (0.00–22.43)	0.00 (0.00–12.27)	0.00 (0.00–9.71)
2003	0.05	0.07	0.20	0.64	0	0.18	0.33	0.41	0.00 (0.00–20.95)	0.00 (0.00–11.19)	0.00 (0.00–8.97)
2004	0.05	0.07	0.21	0.65	3	0.18	0.33	0.43	16.56 (3.33–48.39)	9.15 (1.84–26.73)	7.04 (1.41–20.56)
2001–2004	0.18	0.25	0.78	2.51	4	0.68	1.24	1.57	5.92 (1.59–15.14)	3.23 (0.87–8.27)	2.55 (0.69–6.53)

SIR, standardized incidence ratio; CI, confidence interval; P_b, newborns in Valencia region in millions; P_k, population under k year in Valencia region in millions (k = 1, 5, 15); 0, observed cases; S_b, expected at birth in Valencia region; S_k, expected at k year of age birth in Valencia region (k = 1, 5). The expected cases in Valencia region is obtained under the hypothesis that the global incidence is: expected at birth, 3.7 per million newborns; expected at 1 year of age, 8 per million; expected at 5 years of age, 2 per million.

in watch-dial painters exposed to radium, mesothelioma and lung cancer in asbestos workers, and angiosarcoma of the liver in chemical workers exposed to vinyl chloride.²⁰ Each was recognized as extraordinary by an alert clinician and reported to public health and medical officials for evaluation. In 1970, Herbst diagnosed vaginal clear-cell adenocarcinoma in 7 young women, which led to the identification of diethylstilbestrol as the first transplacental human carcinogen considered.²¹

Until 2005 to 2006, ethylene dibromide, designated by IARC as a probable carcinogen to humans, was used as an antiknock gasoline additive and solvent resin in Spain. Dibenz[a,h]anthracene, a polycyclic aromatic hydrocarbon, found in cigarette smoke or fossil fuel exhaust is classified by IARC as 2A or probably carcinogenic to humans. All gas stations within this study provided leaded and unleaded fuel, as well as diesel fuel. Nickel subsulfide is a known human carcinogen. The major sources of exposure to nickel are fossil fuel combustion and tobacco smoke.²² Also, nickel-gene NTRK interaction has been reported.²³

The highest priority should be given to examining the chemicals that are already known to be carcinogenic or are probable carcinogens in humans. All

patients in this cluster were exposed to nickel and dibenz[a,h]anthracene by tobacco smoke and occupational exposure. If leaded gasoline, containing ethylene dibromide, was consistently used in all the gas stations, then Patients 1, 2, and potentially 3 had a plausible mechanism for exposure via inhalation. There may be a more complex pathway for exposure linking known substances and some substances that are yet unidentified and are associated with fibrosarcoma. No exposure to asbestos was noted in these cases.

We believe that the PEH is the best clinical tool to approximate the etiology of rare pediatric diseases. However, it is not sufficient to meet the Bradford-Hill causal criteria. The use of observational information for exposure assessment is a limitation of these cases studies. Although we recognize that the small sample size limits discussion of causality, we propose that the PEH be elaborated in future cases of CFS. To strengthen our case, we propose to include a more in-depth description of maternal occupation during pregnancy so that estimation of exposure is possible. Additional case-control and experimental studies are needed to confirm the current observations. The highest

priority should be assigned to examining the chemicals that are already known to be carcinogenic or suspected as carcinogenic to humans.

It is important to use the same questionnaire for both cases and healthy controls and to compare how often these same exposures were mentioned among this control group. Recently, we have adapted the PEH-taking tool for use with our obstetrical population.²⁴ Green Page reporting on reproductive environmental health constitutes the standard clinical record of pregnant women and includes a series of concise and basic questions to identify environmental exposures.

In conclusion, a detailed and carefully conducted PEH, which includes information about occupational exposure, should be performed for all cases with CFS. Although future studies are needed to systematically investigate the origins of CFS and its underlying mechanisms, this report suggests that increased occupational safety measures should be considered for all pregnant women.

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