ARTICLE

A Tumor Profile in Edwards Syndrome (Trisomy 18)

DANIEL SATGÉ,* MOTOI NISHI, NICOLAS SIRVENT, AND MICHEL VEKEMANS

Constitutional trisomy 18 causes Edwards syndrome, which is characterized by intellectual disability and a particular set of malformations. Although this condition carries high mortality during prenatal and early postnatal life, some of the rare infants who survive the first months develop benign and malignant tumors. To determine the tumor profile associated with Edwards syndrome, we performed a systematic review of the literature. This review reveals a tumor profile differing from those of Down (trisomy 21) and Patau (trisomy 13) syndromes. The literature covers 45 malignancies: 29 were liver cancers, mainly hepatoblastomas found in Japanese females; 13 were kidney tumors, predominantly nephroblastomas; 1 was neuroblastoma; 1 was a Hodgkin disease; and 1 was acute myeloid leukemia in an infant with both trisomy 18 and type 1 neurofibromatosis. No instances of the most frequent malignancies of early life—cerebral tumors, germ cell tumors, or leukemia—are reported in children with pure trisomy 18. Tumor occurrence does not appear to correlate with body weight, tissue growth, or cancer genes mapping to chromosome 18. Importantly, the most recent clinical histories report successful treatment; this raises ethical concerns about cancer treatment in infants with Edwards syndrome. In conclusion, knowledge of the Edwards' syndrome tumor profile will enable better clinical surveillance in at-risk organs (i.e., liver, kidney). This knowledge also provides clues to understanding oncogenesis, including the probably reduced frequency of some neoplasms in infants and children with this genetic condition.

KEY WORDS: Edwards syndrome; trisomy 18; hepatoblastoma; nephroblastoma; cancer; cancer protection

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INTRODUCTION

Trisomy 18 results in Edwards syndrome [Edwards et al., 1960], which is the second most frequent constitutional autosomal syndrome, occurring in 1/6,000 to 1/8,000 live births. Edwards syndrome is characterized by a constellation of major and minor malformations, growth deficiency, and a marked psychomotor and cognitive impairment [Pont et al., 2006]. Importantly, the condition carries a short life expectancy, with only 5–10% of affected infants living beyond the first year [Cereda and Carey, 2012].

Trisomic conditions—trisomy 18 as well as trisomy 21 (Down syndrome) and trisomy 13 (Patau syndrome)—are associated with a particular distribution of neoplasms [Satgé and Van den Berghe, 1996]. However, the distribution of tumors in Edwards syndrome has not yet been profiled in detail. A better understanding of this distribution will enable appropriate surveillance measures for infants with this condition. We present the first systematic review of the literature describing tumor occurrence in children with Edwards syndrome, with the aim of providing a foundation for clinical follow-up of these children. The findings of these reports reveal a particular distribution of neoplasms that raises questions on oncogenesis in this well-defined genetic

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condition. Surprisingly, it seems that trisomy 18 could protect infants against some of the most common malignancies of early childhood.

Trisomic conditions—trisomy 18 as well as trisomy 21 (Down syndrome) and trisomy 13 (Patau syndrome)—are associated with a particular distribution of neoplasms. However, the distribution of tumors in Edwards syndrome has not yet been profiled in detail. A better understanding of this distribution will enable appropriate surveillance measures for infants with this condition.

MATERIALS AND METHODS

After a previous extensive review of the literature conducted on all autosomal constitutional trisomies [Satgé and Van den Berghe, 1996], one author (DS) followed the literature (PubMed) on tumors in Edwards syndrome for 20 years. We used the terms "Edwards syndrome," "trisomy 18," "neoplasms," "cancer," "benign tumors," without language limitation and whithout limitation of date (i.e., before and after 1996). We excluded hyperplasias and cysts. Case reports from Japan were searched by one author (MN) on Pubmed and Igaku Chuo Zassi (Japanese Central Journal of Medicine), which is a search tool for medical articles written in Japanese and English. All cases found in the Japanese literature were translated to English language by MN.

RESULTS

The search could find 45 cancers and 12 benign tumors in 56 fetuses, infants or children. Five patients has a mosaic trisomy 18 and 1 had both trisomy 18 and type 1 neurofibromatosis.

Hepatoblastoma

Liver cancer is the most frequently reported malignancy in infants and children with trisomy 18. Table I summarizes 29 reports comprising 26 histologically documented hepatoblastomas and three other liver tumors without histological diagnosis. A 30th patient [Bove et al., 1996] insufficiently documented is not included. Patients in this group were ages 3 months to 10 years at diagnosis. Excluding one patient for whom gender was not given, the majority of patients were female (25 vs. 3 males). As hepatoblastoma is more frequent in males in Japan (MN, data from the Japanese government years 2005–2014) this gender distribution may be explained, at least in part, by the better survival of females with trisomy 18 [Cereda and Carey, 2012]. We are not aware of an established susceptibility for hepatoblastoma in Japanese individuals; however, 21/29 patients were reported from Japan. Accordingly, among a series of 43 autopsies performed in infants and fetuses with trisomy 18 in a single Japanese institution, the three reported tumors were hepatoblastoma [Matsuoka and Miaushi, 2000]. This ethnic susceptibility is unique to hepatoblastoma and was not reported for other tumors seen in trisomy 18. Four children had trisomy 18 mosaicism [Tanaka et al., 1992; Takahashi et al., 2004; Fernandez et al., 2011a; Pereira et al., 2012]. This is expected since children with mosaic trisomy 18 have a longer life expectancy compared to children with full trisomy 18. In six children the tumor was an autopsy finding; in some others the tumor was an unexpected finding on routine examination [Maruyama et al., 2001; Pereira et al., 2012] or was discovered during an abdominal ultrasound [Tan et al., 2014]. More commonly, symptoms such as abdominal distention, hepatomegaly, or a palpable mass revealed the tumor. Tumors ranged from 0.3 to 18 cm in diameter, sometimes occupying most of the liver [Ariwa et al., 1992; Ito et al., 2004]. Multiple foci were found in seven children. The histological type was mainly well-differentiated hepatoblastoma or fetal-type hepatoblastoma, rarely embryonal-type hepatoblastoma or mixed fetal-embryonal-type. In one patient the two nodules were slightly different histologically; a molecular examination showed two different clones [Yokoyama et al., 1999]. Interestingly, in one patient the tumor tissue had a 47,XX + 18 karyotype while the normal liver tissue had a 46,XX karyotype [Tanaka et al., 1992]. In contrast, a child with mosaic trisomy 18 exhibited a 46,XX karyotype in tumor cells; the karyotype of normal liver tissue was not indicated [Pereira et al., 2012]. In a third patient the tumor karyotype was complex, with unusual anomalies of chromosome 11 observed in hepatoblastoma [Tan et al., 2014].

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Typical treatment protocols were occasionally modified due to the physical disposition of children with trisomy 18, for example, because of growth deficiency, cardiac insufficiency, or potential renal toxicity of chemotherapy. Some patients did not receive oncotherapy and died from their tumors, or from other causes [Dasouki and Barr, 1987; Maruyama et al., 2001; Ito et al., 2004; Ogawa et al., 2006; Kitanovski et al., 2009]. Conventional or adjuvant chemotherapy was discarded [Teraguchi et al., 1994; Bove et al., 1996; Tan et al., 2014], delivered at lower doses, or abbreviated due to therapy-related complications [Uekusa et al., 2008;

TABLE I. Liver Tumors Documented in Infants and Children With Trisomy 18

Reference	Sex, age	KT	Tumors	Treatment and outcome
Abe et al. [1983a,b]	F, 9 m	Full	Two nodules, well-differentiated hepatoblastoma	Autopsy finding
Mamlok et al. [1989]	F, 4 m	Full	0.4 × 0.3 cm, embryonal-type hepatoblastoma	Autopsy finding
Tanaka et al. [1992]	F, 2 y	Mos	8 × 7 × 6 cm, fetal-type hepatoblastoma	Surgery and chemotherapy. Alive at 9 y 9 m[a]
Ariwa et al. [1992]	F, 8 m	Full	18 × 13 × 5 cm, well-differentiated hepatoblastoma	Chemotherapy (vincristine, endoxan) and radiotherapy. Death 10 m
Teraguchi et al. [1994] Teraguchi et al. [1997] Iiyama et al. [1997] Hamada et al. [1997] Takada et al. [2007]	F, 7 m	Full	9 × 6 × 4 and 4 cm, fetal-type hepatoblastomas	Surgery, chemotherapy discarded. Died 5 y, encephalitis
Bove et al. [1996]	F, 1 y 9 m	Full	9 × 4 cm, fetal-embryonal-type hepatoblastoma	Surgery, bone metastases 5 week after surgery; chemotherapy discarded
Yokoyama et al. [1999]	F, 11 m	Full	Two micro hepatoblastomas	Autopsy finding
Suzuki et al. [1999]	F, 4 m	Full	9 × 8 × 6 cm, well-differentiated hepatoblastoma	Chemotherapy JPLT protocol 91B2 tumor reduction surgery at 1 y 1 m. Alive 8 m after surgery
Hino et al. [1999] Suzuya et al. [2000] Ishibashi et al. [2009] case 1	M, 10 m	Full	5 × 5 cm, well-differentiated hepatoblastoma	No treatment. Death at 1 y 1 m
Uemura et al. [2000a,b]	F, 5 m	Full	Four nodules 2.1, 2.0, 1.7, 0.8 cm, fetal-type hepatoblastomas	Autopsy finding
Matsuoka and Miauchi [2000]	F, 4 m	Full	Multiple tumors 1.5–0.5 cm	Autopsy finding[b]
Nishimura et al. [2000]	F, 6 m	Full	Well-differentiated hepatoblastoma	Autopsy finding
Maruyama et al. [2001]	F, 3 m	Full	2, 4.5, and 3.5 cm, fetal-type hepatoblastomas	No treatment. Died 5 m heart failure
Takagi et al. [2004]	NI, NI	Full	NI	Surgery, age not indicated. Alive 3 m after surgery
Ito et al. [2004]	F, 6 m	Full	Tumor occupied nearly all abdominal cavity, presumed hepatoblastoma	No treatment
Takahashi et al. [2004]	F, 10 m	Mos	7 × 6.4 cm, hepatoblastoma	Chemotherapy (cisplatin, adrianicine), tumor disappearance. Surgery discarded (parents refusal)
Watanabe et al. [2006]	F, 10 m	Full	2.7 × 2.6 cm, hepatoblastoma	Chemotherapy (vincristine and 5-FU no CDDP (renal toxicity). Surgery planed
Nishi et al. [2006]	F, 1 y	Full	3 cm, presumed hepatoblastoma	No surgery, chemotherapy (VP-16). Sudden death 9 days after chemotherapy starting.
Ogawa et al. [2006] Oohashi et al. [2012]	F, 9 m	Full	4 cm, well-differentiated hepatoblastoma	No treatment. Death 10 m, pulmonary hypertension-hypoxia

TABLE I. (*Continued*)

Reference	Sex, age	KT	Tumors	Treatment and outcome
Uekusa et al. [2008] Habu et al. [2009a,b] Uekusa et al. [2012]	M, 1 y 2 m	Full	11.7 × 10.7 cm, fetal-type hepatoblastoma	Chemotherapy THP-ADR CDDR lower doses. Tumor decreases in size. Surgical resection. Postoperative chemotherapy. Alive 1 y 6 m post therapy
Ishibashi et al. [2009] case 2 Ishibashi et al. [2010]	F, 5 m	Full	Four well-differentiated hepatoblastomas	Surgery. Alive at 11 m
Kunikata et al. [2009]	NI, 6 m	Full	Hepatoblastoma	Chemotherapy, Doxorubicin. Death at 7 m
Kitanovski et al. [2009]	F, 6 m	Full	3, 8.3, 3.7, 3.2 cm, fetal-type hepatoblastomas	No treatment. (Parent refusal) death 7 m, probable disease progression
Fernandez et al. [2011b]	M, 9 m	Mos	4.3 × 4.3 × 4 cm, fetal-type hepatoblastoma	Surgery. Chemotherapy cisplatin, 5-FU, vincristine. Two recurrences. Liver transplant. Alive 28 m after transplantation
Pereira et al. [2012]	F, 10 y	Mos	13 × 10 × 8.9 cm, fetal-type hepatoblastoma	Chemotherapy, cispaltin 5-FU, vincristine shortened. Surgery. Alive at 12 y
Sugitate et al. [2012]	F, 2 y	Full	Hepatoblastoma	Surgery. No chemotherapy. Alive 5 m post surgery
Tan et al. [2014] case 1	F, 1 y	Full	6.3 × 6 cm, fetal-type hepatoblastoma stage 1	Complete surgical resection; presurgical chemotherapy discarded
Tan et al. [2014] case 2	F, 7 m	Full	5.3 × 5 × 4.3 cm, feta-embryonal-type hepatoblastoma stage 1	Complete surgical resection. Presurgical chemotherapy discarded. No recurrence. Death at 13 months, cardiopulmonary collapse

NI, not indicated; Mos, trisomy 18 mosaicism; KT, karyotype.
[a]Personal communication with Dr. Teraguchi [1987].
[b]Also had micro nodular hyperplasia adrenals.

Pereira et al., 2012]. Tumor response to chemotherapy was variable, with partial or complete regression [Suzuki et al., 1999; Takahashi et al., 2004; Nishi et al., 2006; Uekusa et al., 2008]. One individual's tumor displayed resistance to 5-fluorouracil (5-FU), which was attributed to the triplication of the *thymidilate synthetase* gene mapping to chromosome 18 [Fernandez et al., 2011b]. Surgery was also discarded in some patients [Hino et al., 1999; Takahashi et al., 2004; Nishi et al., 2006]. Initial reports indicate a poor outcome, except for one long-term survival up to 9 years [Tanaka et al., 1992; Teraguchi et al., 1997]. However, the most recent publications report a better outcome, with survival between 6 and 28 months after various treatments using surgery alone, including one liver transplant, or associated with chemotherapy [Suzuki et al., 1999; Fernandez et al., 2011a; Pereira et al., 2012; Sugitate et al., 2012; Uekusa et al., 2012].

Renal Tumors

Nephroblastoma, reported in 12 children (Table II), is currently the second most frequent solid malignancy in children with trisomy 18. The tumor was usually revealed by an abdominal mass. Table II does not include the observation of a 47, XX + 18 tumor karyotype in a nephroblastoma since the child's phenotype was not reported [Wang-Wuu et al., 1990]. Additionally, nephroblastomatosis has been described as a common feature in kidneys of infants with trisomy 18 [Bove et al., 1969; Scott et al., 2006]. As for hepatoblastoma, there was an imbalance in the female to male ratio of patients. Further, and strikingly, the mean age at diagnosis for the three male patients was 11 months, while the mean age for the nine females was 8 years 2 months. If this age difference is confirmed by further cases, it may suggest that the life expectancy in females does not help to

understand the lack of renal tumors in females under 5 years. In the general population the mean age at diagnosis of renal tumors exhibits a smaller difference: 42 months in males, and 47 months in females [Fernandez et al., 2011a]. In contrast to hepatoblastoma, only one patient was Japanese [Suzuki et al., 1992]. This patient was also the only child with renal tumors who had mosaic trisomy 18. Five patients died from chemotherapy-related sepsis, post-operative cardiopulmonary failure, or advanced disease at diagnosis [Olson et al., 1995; Anderson et al., 2003]. Three other children had prolonged survival to ages 8, 11, and 20 years, one of them despite metastatic disease [Geiser and Schindler, 1969]. Abdominal ultrasounds performed at 15 months of age in a male with large duplication of the chromosome 18q and nearly full Edwards syndrome phenotype revealed multiple cortical renal masses that were not biopsied. The lesions, which could have been nephroblastomatosis or an early Wilms tumor, were successfully treated with 19 weeks of chemotherapy using Daptomycin and Vincristin [Starr et al., 2014]. Additionally, the kidneys of a 4-month-old infant with trisomy 18 contained focal bilateral hamartomas of renal tubules at autopsy [Rosenfield et al., 1962].

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Heart Tumors

Four intracardiac papillary tumors have been reported in three infants and one fetus with documented [Rosenfield et al., 1962; Anderson et al., 1977; Rehder, 1982] or suspected [Flenker, 1972] trisomy 18. These small, benign papillary tumors were situated on the tricuspid or aortic valves, and in one infant on the margin of a ventricular septal defect [Flenker, 1972]. Beyond different names given to these papillary nodules—myxoma, valvular hamartoma, papillary tumor, fibrous vegetations—they presented similar papillary architecture with loose mesenchymal axis devoid of vessels in the three patients with available histology. They differ from polyvalvular diseases frequently reported in patients with Edwards syndrome. Currently, given the potential risk for fatal outcome, these benign tumors are treated by

TABLE II. Kidney Tumors Documented in Infants and Children With Trisomy 18

Authors	Sex, age	KT	Tumors	Treatment and outcome
Geiser and Schindler [1969]	M, 1 y	Full	Typical nephroblastoma	Surgical resection 23 months. Well at 11 y 6m
Karayalcin et al. [1981]	F, 11 y	Full	Nephroblastoma, 15 × 12 cm	Radiotherapy, surgery, chemotherapy, plus radiotherapy on metastases. Death 20 y 5 m cardio pulmonary arrest
Shanske [2006]				
Faucette and Carey [1991]	F, 9 y	NI	Nephroblastoma, NOS	NI
	F, 5 y	NI	Nephroblastoma, NOS	NI
Suzuki et al. [1992]	M, 7 m	Mos	Nephroblastoma, stage I	Surgery and chemotherapy. Death from relapse in the right orbit at 8 y
Olson et al. [1995]	F, 13 y 9 m	NI	Nephroblastoma diffuse blastema, stage III	Death attributed to cancer, unresectable tumor, lung metastases
	F, 5 y 8 m	Full	Nephroblastoma, mixed type stage III	Death, chemotherapy-related sepsis
	F, 8 y 7 m	NI	Nephroblastoma diffuse blastema, stage III	Death, chemotherapy-related sepsis
	F, 5 y 8 m	Full	Nephroblastoma tubular epithelial differentiated stage III	Death, chemotherapy-related sepsis
Kullendorff and Wiebe [1997]	F, 5 y 6 m	NI	Bilateral nephroblastoma, stage V	Death, no treatment
Anderson et al. [2003]	F, 9 y 5 m	NI	Nephroblastoma, stage I	Post-operative death, cardio pulmonary failure

NI, not indicated; Mos, mosaicism; KT, karyotype; NOS, no other specification.

surgical resection [Shahian, 2000]. Papillary intracardiac tumors are very rare during childhood in the general population [Shahian, 2000]. They have not been described in trisomy 13 or trisomy 21. Thus, these cardiac tumors appear specific to Edwards syndrome. Hemangiomas of the pulmonary and mitral valves were reported in a 33-week fetus with trisomy 18 [Shanklin and Sotelo-Avila, 1969].

Skin Tumors

Benign skin tumors have been reported rarely in trisomy 18. A small 0.5-cm capillary hamartoma was observed on the left arm of a newborn female [Townes et al., 1964]. Two pedonculated skin tags were found anterior to the left ear in a 2-month-old female [Smith et al., 1960]. A recent study reported preauricular tags, which are usually considered as malformative benign tumors, in 10% of children with trisomy 18 [Rosa et al., 2013]. A red pedonculated hamartoma occupied the left cheek of a newborn girl who later developed hepatoblastomas [Kitanovski et al., 2009].

Other Tumors

A 4-cm mediastinal solid functional neurogenic tumor (probably a neuroblastoma, a ganglioneuroblastoma, or a ganglioneuroma) was discovered at ultrasound examination of a newborn female. The patient's parents refused treatment. The tumor increased in size, and the patient died at 9 months [Robinson and McCorquodale, 1981]. A stage IB Hodgkin lymphoma has been observed 17-year-old boy with mosaic trisomy 18. He has been successfully treated by usual chemotherapy with four cycles of COPP (cyclophosphamide, vincristin, procarbazine, prednisone/ABU (adriamycin, bleomycin, vinblastine) and local mediastinal radiotherapy with a total dose of 14.4 Gy [Motta et al., 2016]. In the digestive tract, an adenomyosis of the stomach and a jejunal polyp, respectively, were discovered at autopsy of a 3-day-old and a 16-day-old infant [Kinoshita et al., 1989]. The pancreas of a 7-day-old male contained a microcystic adenoma [Hashida et al., 1983]. Proliferative hamartomatous lesions have been described in pancreas of fetuses [Rehder, 1982]. The testes of one fetus contained gonadoblastoma-like tubular hamartomas [Coerdt et al., 1985]. Two adrenal lesions, which are not true neoplasms, have been observed in trisomy 18, a cortical micronodular hyperplasia in a 4-month-old [Matsuoka and Miauchi, 2000], and cytomegaly of the fetal adrenal cortex in a 3-day-old [Bove et al., 1969]. Finally, a 17-month-old Japanese female with trisomy 18 and likely associated type 1 neurofibromatosis died from juvenile myelomonocytic leukemia [Tateishi et al., 2005]. No information was provided on treatment. This hematopoietic malignancy is strongly associated with type 1 neurofibromatosis. It is one of the two hematopoietic malignancies we uncovered in this review.

DISCUSSION

Tumor Frequency and Distribution

The frequency of tumors in Edwards syndrome is not known. Given the prevalence of trisomy 18, estimated at around 1/6,000 live births, and the incidence of pediatric cancer in 1/500 children under 15 years, the 45 cancers identified in this systematic review suggest that malignancies are rare. This would be particularly true if we exclude the 23 Japanese cases. One study on cancer in children with birth defects found no case of cancer in the small cohort of 378 infants with trisomy 18 [Botto et al., 2013]. The fact that just 5–10% of infants with trisomy 18 live beyond the age of 1 year may explain the small number of observed tumors. It is also possible that some tumors are not reported in the literature. However, a systematic and extensive examination of organs in fetuses [Rehder, 1982; Coerdt et al., 1985] and in newborns [Kinoshita et al., 1989] uncovered benign tumors, indicating that proliferation anomalies are not so rare in Edwards syndrome. On the other hand, clinicians are more prone to report patients with Edwards syndrome and a malignancy than patients without a malignancy. This bias must be kept in mind for the evaluation of tumor frequency in Edwards syndrome. On the basis of the few reported cases, and until a large international study is available, we conclude that cancer could be relatively rare in infants with Edwards syndrome.

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It is not easy to evaluate the tumor profile of a particular condition on the basis of case reports and small series only. However, since no large series or large epidemiological study yet exists, there is value in determining the tumor types in Edwards syndrome. In assuming that the cancer distribution is similar in infants and children with Edwards syndrome and in the general population, we would expect at least a few instances of the most frequent pediatric malignancies [Scheurer et al., 2011]. Yet, the 45 malignant tumors summarized in this review do not support this hypothesis. Brain tumors are the most frequent solid tumors in childhood, accounting for more than 20% of all neoplasms [Scheurer et al., 2011], but no brain tumor has been described in a fetus, infant, or child with trisomy 18. Leukemia, which is the predominant malignancy in children under 15 years and accounts for 25% of cancers, has not been reported in a child with pure trisomy 18 [Tateishi et al., 2005].

Neuroblastoma, the third most frequent malignancy in children (7% of cancers) in the general population [Scheurer et al., 2011], has been reported only once [, 1981]. Additionally, no germ cell tumor such as teratoma, usually observed in infancy or early childhood, has been described in a fetus or a child with Edwards syndrome, though germ cell tumors are reported in trisomy 21 [Satgé et al., 2003] and in trisomy 13 [Satgé and Van den Berghe, 1996].

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Despite the poor survival of infants with Edwards syndrome, we gathered 57 reports of benign (12) and malignant (45) neoplasms. The compilation of these reports indicates a particular tumor profile compared to that occurring in normal fetuses, infants, and children. Hepatoblastoma and nephroblastoma, which together make up nearly 5% of all malignancies in euploid children [Scheurer et al., 2011], account for 38 of the 41 malignancies with documented histology reported in children with trisomy 18. Conversely, the most frequent malignancies of childhood—brain tumors, leukemia, neuroblastoma, and germ cell tumors—which make up more than 65% of childhood tumors [Scheurer et al., 2011], are strikingly underrepresented. One neuroblastic tumor and one Hodgkin lymphoma are reported in this population; the other common cancers are not reported. This tumor profile also differs from that of children with Down syndrome, in whom leukemia, germ cell tumors, and retinoblastoma are more frequent than in the general population, and hepatoblastoma and nephroblastoma are unusually rare [Satgé et al., 1998a; Satgé et al., 2003]. Further, the profile differs from that of children with Patau syndrome (trisomy 13), in whom neuroblastoma, germ cell tumors, cerebral tumors, epithelial tumors, and renal tumors are the most frequently reported malignancies [Satgé and Van den Berghe, 1996].

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Tumor Causes

Malformations

A link between cancer, particularly in childhood, and malformations has long been suspected [Bleeker et al., 2014]. Cardiac tumors, particularly papillary neoplasms, are very rare in children. Thus, reports of five affected infants in a syndrome where cardiac malformations are estimated to be 120-fold more frequent than in the general population [Pont et al., 2006] would suggest a link; however, cardiac papillary tumors are benign proliferations. On the other hand, hepatoblastoma is the most frequent malignancy in children with trisomy 18, but hepatobiliary malformations are not common in Edwards syndrome; indeed, few cases have been reported [Ikeda et al., 1999, Kahramaner et al., 2013]. The second most frequent type of cancer in trisomy 18 is renal, whereas the risk for urinary tract malformation is one of the lowest (8.7%) among various organ systems investigated [Pont et al., 2006]. Finally, despite a 62-fold increased risk for central nervous system malformations in trisomy 18 [Pont et al., 2006], not a single case of cranial tumor has been reported. Thus, the link between cancer and malformation does not seem conclusive in this context.

Abnormal growth

The risk for hepatoblastoma is increased through an unknown mechanism among children with low birth weight and particularly with very low birth weight, [Spector et al., 2009]. Thus, the rate of hepatoblastoma in trisomy 18 is probably linked to prenatal and postnatal growth retardation, which characterizes Edwards syndrome [Cereda and Carey, 2012]. One study found a possible slight excess of retinoblastoma and glioma as well as a reduced frequency of Wilms tumors in very low birth weight children [Spector et al., 2009]. As this tumor distribution has not been observed in our review, the body weight of children with trisomy 18 does not seem able to explain the observed tumor profile. On the other hand, two evaluations of visceral growth and weight in mid-gestation fetuses [Barr, 1994] and newborns [Naeye, 1967] found that the spleen and kidneys are over-weighted in individuals with trisomy 18. As kidney over-weight/nephromegaly and nephroblastomatosis favor Wilms' tumor [Fernandez et al., 2011b], kidney development in trisomy 18 could be a risk factor for embryonal renal tumors.

Supernumerary chromosome 18 and supernumerary genetic material

Trisomy 18 within tumors as a sole abnormality or associated with other tumor karyotype abnormalities is considered non-specific [Van Dyke, 2003]. Trisomy 18 has been found mainly in hematopoietic malignancies such as acute and chronic lymphocytic leukemia, lymphomas, and multiple myeloma [Van Dyke, 2003]. It has also been observed in non-hematopoietic tumors such as breast cancer in adults [Bullerdiek et al., 1994], the benign cutaneous tumor pilomatricoma in children

[Agoston et al., 2010], and other tumors. As children with Edwards syndrome have a short life expectancy, it is not possible to evaluate whether constitutional trisomy 18 increases the risk of adult tumors. Nonetheless, as our review yielded only one case of hematopoietic tumor, although these tumors are the most frequent cancers in children in the general population, a lack of clear correspondence between constitutional and tumor karyotype is likely. This challenges the direct link between constitutional and tumor karyotype predicted by the somatic mutation theory of cancer. For instance, the increased expression of *MIB1* and *BCL2* genes, which map to chromosome 18, should increase the risk for hematopoietic tumors [Van Dyke, 2003]. The evidence does not support this. Benign tumors, like a microcystic adenoma [Hashida et al., 1983] and pancreatic hamartoma-like lesions [Rehder, 1982], have been found in a newborn and in fetuses with trisomy 18. Interestingly, a team has shown that *GATA6*, which maps to chromosome 18 and is a regulator of gene expression and function of the normal pancreas, is amplified in pancreato-biliary cancer [Kwei et al., 2008]. Actually constitutional trisomy induces more complex variations in transcription with a particular transcriptional response pattern independent of the type of aneuploidy, possibly involved in carcinogenesis [Dürrbaum et al., 2014]. However, the role of these anomalies remains to be understood to explain the very different tumor distribution observed in constitutional trisomy 13, 18, and 21.

Aneuploidy has been proposed to favor oncogenesis by increasing chromosome instability in human cells [Duesberg et al., 2011]. If this mechanism is effective, we should expect an excess of cancer in constitutional aneuploidies such as autosomal trisomies, in which all cells have the same supernumerary autosome. Such global excess of cancer has not been observed in trisomy 21 [Satgé et al., 1998a; Hasle et al., 2000]. The small number of malignant tumors summarized in this review does not suggest an increased frequency of cancers in individuals with trisomy 18. Indeed, the rarity of some tumors in individuals with trisomy 18 or trisomy 21 [Satgé et al., 1998b, 2001, 2013] argues against an increased tumorigenesis. A recent experiment showed that various constitutional trisomies, including trisomy 18, induce moderate chromosome instability that is estimated to be insufficient to generate cancer-like levels [Valind et al., 2013].

Treatment, Tumor Screening, and Ethical Problems

Therapeutic successes reported for hepatoblastoma, nephroblastoma and Hodgkin lymphoma show that cancer treatment is possible for infants and children with trisomy 18, with survival of 9 years after surgery for nephroblastoma and at least 2 years for hepatoblastoma. The high risk for these tumors in children with trisomy 18 who survive the first week of life prompted a recommendation for periodic screening with abdominal ultrasounds every 6 months [Carey et al., 2002; Cereda and Carey, 2012]. Given the short life expectancy of newborns with Edwards syndrome, it has been suggested that invasive procedures and surgery may be avoided for these children [Goc et al., 2006]. However, treatment may be considered in a context of collaborative physician–parent decision-making, taking into account the benefits, and burdens of care options [Lorenz and Hardart, 2014]. Treatment with surgery, chemotherapy, and radiotherapy should be the same as for ordinary children, when possible, particularly for milder phenotypes. It should be adapted case by case for children who have particular organ and/or metabolic weaknesses.

We recognize that this systematic review lacks the power of an epidemiological study for assessing the tumor profile in trisomy 18. There is an over-representation of Japanese reports. A control with trisomy 21 using the same method showed only few additional cases of tumors frequent in Down syndrome, intracranial germ cell tumors, and testicular cancer. Another control with trisomy 13 reveal only two tumors not reported in Pubmed. We believe that numerous cases of hepatoblastoma in this review reveal a specific excess of this tumor in Japanese infants and children with trisomy 18. Further, other publication bias may not produce an accurate representation of tumor occurrences. We hope that this review will prompt pediatricians to report their experiences to help overcome such limitations in the future. A systematic review of published cases in fetuses, children, and adults with Down syndrome [Satgé et al., 1998a] was largely confirmed by epidemiological studies reported during the following decade [Hasle et al., 2000; Patja et al., 2006; Sullivan et al., 2007], demonstrating that important foundation provided by such studies.

CONCLUSION

This first systematic review of tumors in Edwards syndrome reveals a particular distribution of malignancies. While awaiting a large international study that has the power to extend the knowledge of the tumor profile in individuals with trisomy 18, the collected data are useful for two main reasons. The first is that they can enable an understanding of how a supernumerary copy of genes on chromosome 18 favors a given subset of tumors, and seem to protect against other tumors. A simple correlation with data on tumor genetics as predicted by the somatic mutation theory of cancer is not likely. The oncogenetic mechanism could be more complex through chronic functional and metabolic modifications on tissues that could lead to malignant transformation. The second reason, and most important from a medical point of view, is that knowledge of the particular distribution of cancers will enable better medical follow-up of children with Edwards syndrome. Direct surveillance of at-risk organs will promote an earlier tumor diagnosis, especially for liver and kidney tumors. The reports that document successful

treatment justify an adapted tumor surveillance when treatment is considered, taking into account all aspects of the condition.

This first systematic review of tumors in Edwards syndrome reveals a particular distribution of malignancies. While awaiting a large international study that has the power to extend the knowledge of the tumor profile in individuals with trisomy 18, the collected data are useful for two main reasons.

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