A Lack of Neuroblastoma in Down Syndrome: A Study from 11 European Countries


ABSTRACT

An epidemiological investigation in 11 European countries comprising a total childhood population of 54.1 million children and using 8 separate data sources was conducted to evaluate the occurrence of neuroblastoma in Down syndrome (DS). No cases of DS were detected among 6724 infants and children with neuroblastoma, although more than five were expected. This highly significant result ($P \approx 0.0045$ according to the Poisson test) is consistent with data in the literature, which contains only two poorly detailed cases in epidemiological studies and one ganglioneuroma in a DS mosaic patient. Like other tumors, such as leukemias, testicular germ cell tumors and lymphomas are in excess in DS patients; the lack of neuroblastomas does not reflect a general decreased incidence of cancer but rather a specific underrepresentation of this precise tumor.

INTRODUCTION

An association between congenital anomalies and childhood cancers is now clearly demonstrated; thus, a better knowledge of this link may help identify genes involved in cancer development (1). Among genetic diseases, there are several, such as DS, neurofibromatosis type 1, Beckwith-Wiedemann syndrome, and tuberous sclerosis, which are associated with an excess of various neoplasms (2). As far as we know, a decreased incidence of a specific neoplasm in a particular genetic disease has never been reported. An updated review of the literature on solid tumors in DS patients (3) yielded only two cases of neuroblastoma (4,5) and one ganglioneuroma (6). Because neuroblastoma is the most frequent solid cancer found in children before the age of 5 years, accounting for 6 to 10% of all childhood cancers (7), we suspected that this finding could be the indication of a lower incidence of this neoplasm in this constitutional chromosomal anomaly. We investigated this hypothesis by studying a series of more than 6000 cases of neuroblastoma compiled in 11 European countries.

MATERIALS AND METHODS

Cases were identified in 11 European countries, 6 of them through pediatric cancer registries: the British National Registry on Childhood Tumors for Great Britain; the German Childhood Tumor Registry for Germany; and the Nordic Childhood Cancer Registry for Finland, Iceland, Norway, and Sweden. The data from Denmark came from the Danish Cancer Registry. In Germany, the National Childhood Cancer Registry began in 1980, and coverage was less complete in the early years (8). These German data include only the former West Germany and not East Germany before reunification. In the Netherlands, cases came from the four regional pediatric oncology centers that cover the whole geographic area. The Swiss data about incidence of pediatric cancer were provided through the network of the Swiss Pediatric Oncology Group, which includes all ($n = 8$) Swiss institutions involved in the management of childhood cancer in this country. In Switzerland, this coverage is considered to be close to 100%. In France and Italy, cases were gathered from centralized sources that hold data on children with neuroblastoma who are seen in France by the members of the Société Française d’Oncologie Pédiatrique and in Italy by the members of the Cooperative Group for Neuroblastoma. These two data sources are considered to cover 95% of the whole population. To gather as many cases as possible, we included the longest period available for each registry or centralized data source varying from 5 to 48 years. Although the upper limit for age varied according to each registry, inclusion of the age range between 14 and 18 years does not lead to any substantial problem, given the fact that neuroblastomas occur mainly before 10 years of age (7). Eligible cases were those diagnosed as histologically proven peripheral neuroblastomas, including, for some registries, in situ neuroblastomas and central nervous system neuroblastomas. In situ neuroblastomas are minute, incidentally encountered adrenal neuroblastomas usually found during autopsies of infants (9). In five national registries, systematic recording of the conditions associated with each case is provided, permitting the detection of DS cases. In the others, systematic registration was not indicated, but major malformations were mentioned, and it was possible to indicate the presence or absence of DS in children. Moreover, cancer treatment for a DS patient raises difficult therapeutic problems due to enhanced drug toxicity (well documented for leukemias; Ref. 10), which would have attracted the attention of clinicians and alerted them to the condition. For comparison purposes, we checked the presence of three other conditions clinically associated with neuroblastomas: neurofibromatosis type 1, Hirschsprung’s disease, and Beckwith-Wiedemann syndrome (11,12).
We evaluated the DS population based on the rate at birth as indicated by the European Registry of Congenital Anomalies (13), which gives the crude rates during the years 1990–1994 in the 25 registries at around 10.4 DS per 10,000 live births (or one for 961.5 births). Because prenatal screening has improved during the last decade (14), we think that this value underestimates the DS population at birth for the first years of the study. Life expectancy is lower in individuals with DS compared to the general population, with only 76.6% of individuals still alive at age 15. This allowed us to calculate a minimum estimate of the proportion of the population ages 0–14 years with DS in the study regions (15).

We used the Poisson statistic test to compare the number of cases of neuroblastoma observed in the DS population with the number expected based on general population rates.

RESULTS

Table 1 shows that no case of DS was found among 6724 cases of neuroblastoma. Taking the rate of occurrence of DS as 1 in 961.5 live births and the survival rate to age 15 as 76.6%, at least 5.40 cases of DS would be expected among 6724 cases of neuroblastoma. The Poisson probability of observing no case is 0.0045. This estimation is conservative, taking into account the fact that most neuroblastoma cases occur before 10 years of age and that 78.4% of DS children survive that age. By allowing in our population older subjects at a very low risk of neuroblastoma, we may underestimate the expected figure, thereby diluting slightly the observed effect.

Because the incidence of neurofibromatosis type 1 is estimated at 1 in 3,000 individuals (16), and because some cases are sometimes not diagnosed before 15 years of age, the 19 cases observed in the study show an important excess of neurofibromatosis cases in this condition, as expected. Similarly, because the incidence of Beckwith-Wiedemann syndrome, which is usually diagnosed in the first months of life, is estimated to be 1 in 13,700 (17) the four cases observed in this study show an important excess of neuroblastomas in this condition, as expected. Because Hirschprung’s disease occurs in approximately 1 in every 5,000 infants born alive births and its diagnosis is made mostly during the 1st year of life (18), the only case observed in this study does not support the idea of an excess of neuroblastoma in this condition. Taken together, these results indicate that in this population of 0–18 years of age, infants and children with diseases known to be at risk for this nervous system neoplasm were not missed.

DISCUSSION

This study failed to detect a single case of DS among 6724 infants and children with neuroblastoma, whereas according to our estimation of the DS population, more than 5 cases were expected. This result is highly significant but has to be discussed regarding possible biases, particularly the possibility of undeclared DS cases. The eventuality of unrecognized DS among neuroblastoma patients is unlikely, because this syndrome is clearly visible and clinically identifiable (19) with an easy cytogenetic verification. More subtle and rare malformative conditions and syndromes are recorded (12) in some registries. A second possibility is the underdiagnosis and undertreatment of a malignancy such as neuroblastoma in this genetic disorder. This is also unlikely: the well-known excess of leukemia argues against a general underdiagnosis of malignant conditions in DS patients. Furthermore, clinicians will be alerted because of the difficulties of clinical and complementary examinations due to the mental impairment of these patients (20), as well as treatment problems due to enhanced drug toxicity in the case of leukemias (10) and solid tumors (21). For these reasons, it is unlikely that a DS case would be overlooked by a team or a clinician. A third possibility is the lack of registration of recognized DS cases. This does not apply to the 5386 cases included in the registries in which registration of associated malformations is systematic. This is also not likely for the other 1338 cases (all cases from West Midlands, United Kingdom, before 1970; fewer than half of the French cases; and all cases from the Netherlands, Finland, Iceland, Norway, and Sweden), because major prob-

<table>
<thead>
<tr>
<th>Country</th>
<th>Period covered</th>
<th>Age range for inclusion in the registry</th>
<th>Number of neuroblastomas</th>
<th>Systematic registration of associated conditions</th>
<th>NF</th>
<th>BW</th>
<th>HD</th>
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Cases of neurofibromatosis type 1.
Cases of Beckwith-Wiedemann syndrome.
Cases of Hirschsprung’s disease.
Cases of DS.
Localized disease and metastatic disease under 1 year of age.
In situ neuroblastomas included.
Metastatic disease after 1 year of age.
Central nervous system neuroblastomas included.
West Midlands.
Amsterdam area.
Nijmegen area.
Groningen area.
Rotterdam area.
Cases of neurofibromatosis type 1, Beckwith-Wiedemann syndrome, and Hirschsprung’s disease expected (age not adjusted).
Cases of DS expected (age adjusted).

Table 1. Cases of DS compared to cases of neurofibromatosis type 1, Beckwith-Wiedemann syndrome, and Hirschsprung’s disease in a European series of neuroblastomas

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problems with diagnosis and treatment were mentioned. In addition, Table 1 includes 19 cases of neurofibromatosis type 1, 1 of Hirschsprung's disease, and 4 of Beckwith-Wiedemann syndrome, indicating that congenital abnormalities were not being missed. A fourth possibility would be missing a neuroblastoma in a DS child who died of some other cause. This is probably also unlikely to happen, but, given the incidence of in situ neuroblastomas in some autopsies of children with congenital anomalies (9), it does need to be considered. Therefore, we believe that the results strongly suggest a decreased incidence of neuroblastomas in the DS population.

These results are in agreement with a previous search of the literature. There is only one ganglioneuroma published as a case report in a mosaic DS patient (6) and two neuroblastomas included in a series of childhood tumors associated with malformations (4, 5). These last cases are very poorly documented; one is found in an epidemiological series at a time when the various kinds of childhood small round cell tumors were not well differentiated (4), and it is not possible to completely exclude a nonneuroblastoma case registered as a neuroblastoma. Finally, after a careful manual and computer search, we could not find a single well-documented neuroblastoma in a nonmosaic DS subject. Two series of 1632 neuroblastomas (22, 23) and a compilation of malformations associated with neuroblastomas (24) contained no trisomy 21 cases. Similarly, no case of neuroblastoma was found among 135 DS children with cancer in the British Registry of Childhood Tumors (2), whereas this cancer accounts for 6–10% of childhood neoplasms in the Caucasian population. Our data are also interesting, because this is the first large study in a European region with populations as different as those of Italy and the Nordic countries. In situ neuroblastoma, the incidence of which is estimated to be 40–50 times higher than florid neuroblastoma (11), has been observed with various malformations (9, 25) including trisomy 13 (26) and trisomy 18 (27). To our knowledge, it has never been reported with trisomy 21, which is, however, much more common. Finally, besides trisomy 13 and 18, neuroblastoma has been observed with various exceptional constitutional chromosomal anomalies (28, 29). On the other hand, it is well accepted that DS individuals have a 20–30-fold excess risk of leukemias, particularly of the M7 type (30). They may possibly also have more lymphomas (31, 32) and testicular germ cell tumors (21, 33) than the general population. Thus, the supposed decreased incidence of neuroblastoma does not reflect a general decrease of cancers in individuals with DS, but rather suggests a possible specific phenomenon concerning this particular peripheral nervous tumor.

A modification of a neoplasm incidence rate may result from a genetic impairment, from environmental factors, or from a combination of the two (34). Several genetic disorders have been described in association with neuroblastomas: neurofibromatosis type 1, Beckwith-Wiedemann syndrome, Hirschsprung's disease, Turner syndrome, Duchenne's muscular dystrophy, and cystic fibrosis. Furthermore, homozygous deletion of neurofibromatosis 1 gene has recently been observed in a primary human neuroblastoma (35). The first two conditions are most likely to represent risk factors, but at the present time, no definitive relationship between a higher risk of neuroblastoma and a genetic disease has been proven (11, 12). Genetic factors have been evoked to explain some ethnic variations in the incidence of neuroblastomas (36, 37). More recently, it has been proposed that the underlying risk could well be the same in all populations and that variations in recorded incidence simply reflect variations in the proportions of tumors that are diagnosed and registered (37). We are not aware of any work suggesting a lower risk of developing neuroblastoma in a particular genetic disease (38).

Several gestational factors have been considered either in isolated case reports or in analytical epidemiological studies (11, 12, 23, 34, 39). A risk has been suggested in the offspring of mothers at the extremes (young or old) of their childbearing age (34) and after exposure to sex hormones (39). Because early or late childbearing age is a well-known risk factor for trisomy 21 (19) and because exposure to sex hormones is a suspected risk factor for trisomy 21 (40), we would expect a higher incidence of neuroblastoma in individuals with DS compared to the general population. Given the lack of strong environmental or other types of external confounding factors and given the major repercussions of the supplementary chromosome on the DS phenotype, we consider that a genetic mechanism is probably also involved in the rarity of neuroblastomas in individuals with DS.

The DS phenotype is the result of an imbalance due to an excess of genetic material on the supernumerary chromosome 21. A parental imprinting mechanism is theoretically possible, but it has not been observed, at least postnatally, for chromosome 21 (41). The dysregulation of one or more genes situated on other chromosomes has been seen in an animal model of DS (42). This implies that it is not possible to exclude, a priori, the role of a gene that is not situated on chromosome 21 in certain aspects of DS. However, the most probable mechanism is an overproduction through gene dosage effect of proteins, the genes for which map to chromosome 21 (43). We propose that chromosome 21 may have a protective effect against neuroblastoma by inhibiting the onset and/or the growth of the tumor. Because central issues in molecular cancer research include to find out whether particular genetic alterations can provide information that is of diagnostic and prognostic value (44), we think that this observation is important. It is interesting to note that three recent studies on neuroblastoma genomic imbalances using comparative genomic hybridization showed that gain of chromosomal material is much more often found in neuroblastoma cells than are chromosome losses (45–47). All of these investigations found that gain of chromosome 17 material is the most common aberration detected in 63–75% of investigated cases. Moreover, extra material from chromosome 21 was not found in any investigated tumor in these independent studies, whereas the phenomenon of additional chromosomal material could be detected for all other chromosomes in several tumors.

On the distal part of the long arm of chromosome 21 maps the S-100 b gene (48), which fills many conditions for being implicated, at least in part, in the lack of neuroblastomas in individuals with DS. A previous work (49) discusses the following arguments more extensively: S-100 b protein, the dimeric product of the gene, is secreted principally in glial cells and nonneural cells of the peripheral nervous system (50) and induces differentiation of neural cells in vitro (51). S-100 b protein is overproduced in blood plasma (52) and nervous tissues (53) in patients with DS. A comparative study of 44 DS patients and 28 controls showed a clear excess of serum S-100 b protein (160 pg/ml) compared to controls (76 pg/ml; P < 0.001; Ref. 52). An immunohistochemical study suggested that the amount of S-100 protein in astrocytes of DS brains was even greater than the 1.5-fold expected (53). This protein is abundant in the stroma of well-differentiated neuroblastomas with good prognosis and is rare or absent in undifferentiated neuroblastomas of very poor outcome (54). Protein S-100 b induces inhibition of growth and death of several human and murine neuroblastoma cell lines in vitro (49, 55–57).

Several observations indicate an underdevelopment of the peripheral nervous system in individuals with DS, with a reduced number of neurons in esophageal plexus ganglia (58) and tooth agenesis, which is probably related to impaired mandibular innervation (59). Furthermore, autopsy studies of children with DS disclosed fairly hypoplastic changes of the adrenal medulla, which is considered as a sympathetic ganglion (60–62). It is tempting to speculate that this inhibition of growth of the nervous tissue could also result from a moderate but chronic overproduction of S-100 b protein, which in-
hibits neural cell growth and enhances differentiation, in prenatal (53, 63) and postnatal life (52). A unifying model would be that in individuals with DS, the overproduction of S-100 b protein through a gene dosage effect could produce both a deleterious effect on peripheral nervous tissue and a beneficial effect, inhibiting the onset and/or the growth of neuroblastomas.

Because the level of differentiation in neuroblastoma is of great importance for the response to treatment (64), we think that a protein inducing neuroblastoma cells and inhibition of growth, differentiation, and death in vitro is a good candidate to explain the rarity of this tumor in a disease in which it is overproduced. However, because cancer is a multistep process, we do not exclude the possibility that other factors and possibly other genes on chromosome 21 act together to prevent the development of this neuroectodermal tumor in people with DS. For instance, several genes of the IFN system map to the long arm of chromosome 21, whereas IFN has extensive and quite diverse effects on nervous tissues (65). If S-100 b protein is effective in decreasing the incidence of neuroblastomas in individuals with DS, it could be very interesting to see, at least in some patients with sporadic neuroblastoma, whether there was a quantitative or qualitative anomaly of this protein or its biochemical pathways. Also, we wonder whether S-100 b protein could not be used as a differentiation inducer to treat neuroblastomas and even to prevent the onset of neuroblastomas in conditions at risk, when they will be known.

We conclude that this large study clearly demonstrates the lack of neuroblastoma in people with DS. This is in full agreement with the literature research we conducted. To our knowledge, this is the first time that a genetic disease has been linked with the lack of a precise tumor. This model may be the paradigm of a particular approach of the decreased incidence of some neoplasms in genetic diseases. It can be applied to other tumors that are underrepresented in those with DS and to other genetic diseases. More specifically, our results are in favor of a protective effect of chromosome 21 against neuroblastoma development, as supported by recent genetic studies using comparative genomic hybridization. However, at the present time, to confirm these data and our interpretation, more epidemiological and experimental studies are needed, such as genetic transfer involving whole chromosome 21, chromosomal regions, or expression vectors for specific genes, including the gene S-100 b.

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