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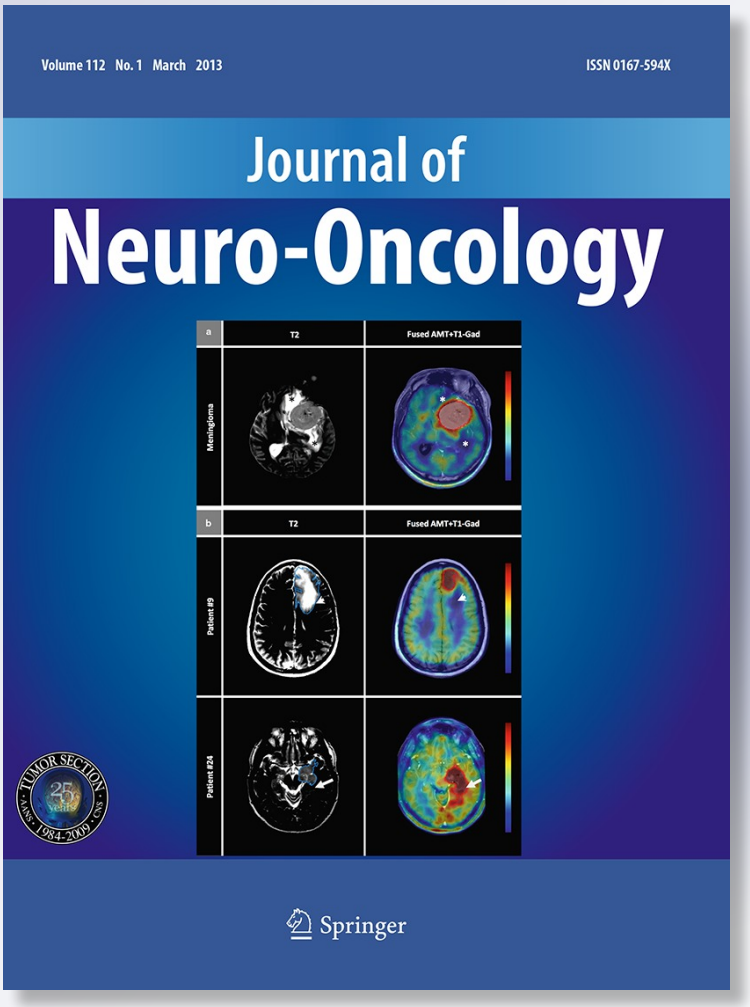

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CLINICAL STUDY

A very rare cancer in Down syndrome: medulloblastoma. Epidemiological data from 13 countries

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Abstract Persons with Down syndrome (DS) uniquely have an increased frequency of leukemias but a decreased total frequency of solid tumors. The distribution and frequency of specific types of brain tumors have never been studied in DS. We evaluated the frequency of primary neural cell embryonal tumors and gliomas in a large international data set. The observed number of children with DS having a medulloblastoma, central nervous system primitive neuroectodermal tumor (CNS-PNET) or glial tumor was compared to the expected number. Data were collected from cancer registries or brain tumor registries in 13 countries of Europe, America, Asia and Oceania. The number of DS children with each category of tumor was treated as a Poisson variable with mean equal to 0.000884 times the total number of registrations in that category. Among 8,043 neural cell embryonal tumors (6,882 medulloblastomas and 1,161 CNS-PNETs), only one patient with medulloblastoma had DS, while 7.11 children in total and 6.08 with medulloblastoma were expected to have DS. (p 0.016 and 0.0066 respectively). Among 13,797

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children with glioma, 10 had DS, whereas 12.2 were expected. Children with DS appear to be specifically protected against primary neural cell embryonal tumors of the CNS, whereas gliomas occur at the same frequency as in the general population. A similar protection against neuroblastoma, the principal extracranial neural cell embryonal tumor, has been observed in children with DS. Additional genetic material on the supernumerary chromosome 21 may protect against embryonal neural cell tumor development.

Keywords Brain tumor · Down syndrome · Glioma · Medulloblastoma · Natural protection against cancer · Primitive neurectodermal tumor

Introduction

Observations of increased frequencies of cancer in people with a wide range of genetic conditions have led to important discoveries in the genetic basis of cancer. There is mounting evidence that decreased frequencies of cancer associated with other complex diseases could also be highly informative [1]. Accumulated data on cancer in patients with Down syndrome (DS) since the 1960s indicate that they have a unique tumor profile [2], with an increased frequency of leukemia but a decreased risk of solid tumors [3, 4]. This broad description obscures more complex variations in the frequency of tumors, and sometimes between different tumor types in the same organ. In fact, compared to the general population, some solid tumors are less frequently observed in patients with DS, some are seen with roughly the same frequency, and conversely still others are more frequent. This particular distribution may remain unrecognized unless each tumor subtype is carefully evaluated. For instance, in the central nervous system (CNS) it is suspected that persons with DS have an increased risk of germ cell tumors and of mesenchymal tumors, whereas the frequency of glial tumors seems to be similar to that in the general population [5]. On the other hand, preliminary evidence suggests they may have a reduced risk of neural tumors such as medulloblastomas and central nervous system primitive neurectodermal tumors (CNS-PNETs) [6].

Medulloblastomas and CNS-PNETs are embryonal tumors composed of undifferentiated or poorly differentiated neuroepithelial cells which share an early onset and an aggressive behaviour [7, 8]. Together they are the second most common group of CNS neoplasms encountered among children, accounting for nearly 20 % of all brain tumors in children [9, 10]. Establishing the rarity of CNS neural tumors in a well defined genetic condition could serve as a valuable basis for research on biological factors that might reduce the incidence of particular tumors. Thus, we sought to estimate the frequency of medulloblastomas and CNS-PNETs in children with DS by collating data from cancer registries in 13 countries across four continents.

Method

Data sources

Data were collected from 15 different sources in 13 countries of Europe, America, Asia and Oceania (Table 1). For seven countries the source was a national population based childhood cancer registry i.e. Argentina, Australia, France, Hungary, Japan, Switzerland and the United Kingdom. For Denmark the source was a population based general cancer registry including children and adults. For Canada and Spain the source was a population based regional childhood cancer registry. Two institutional childhood cancer registries provided data for Italy. For Austria and Germany data were obtained through the population based trial office for malignant childhood brain tumors. Together, these registries cover a total general population of 461.9 million people (see Table 1). The period covered varies between 39 years (1968–2006) for Denmark and 9 years (2000–2008) for

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Table 1 Registries questioned to evaluate the association between medulloblastomas and central nervous system primitive neurectodermal tumours with Down syndrome

Countries	Registry name	Included population	Registration rate	Covered period	Age (years)
Argentina	Argentinian oncopediatric hospital registry	Whole country 36.6 M	100 %	2000–2007	0–14
Australia	Australian pediatric cancer registry	Whole country 21.9 M	100 %	1983–2006	0–14
Austria	Austrian brain tumour registry/HIT program	Whole country 8.4 M	90 %	1991–2007	0–18
Canada	Pediatric oncologic group of Ontario Network information system	Ontario province 11.4 M	98 %	1985–2007	0–14
Denmark	Danish cancer registry	Whole country 5.3 M	100 %	1968–2006	0–14
France	French national childhood solid tumour registry	Whole country 58.9 M	100 %	2000–2008	0–14
Germany	Program Hirntumor (HIT)	Whole country 85.0 M	>95 %	1987–2009	0–21
Hungary	Hungarian pediatric cancer registry	Whole country 10.2 M	99 %	1983–2009	0–14
Italy 1	Tumor national institute IRCCS	Lombardia province 9.0 M	NA	1987–2011	0–21
Italy 2	Children's cancer registry Hospital Giannina Gaslini	Liguria province and south Italy 6.0 M	NA	1987–2008	0–14
Japan	Japan Children's Cancer Registry	Whole country 126.7 M	60 %	1969–2006	0–14
Spain 1	Childhood cancer registry (Comunitat Valenciana)	Provinces of Alicante, Castellon and Valencia 4.1 M	100 %	1983–2006	0–14
Spain 2	National childhood cancer Registry Spain	Province of Barcelona Catalonia 12.1 M	92 %	1990–2006	0–14
Switzerland	Swiss childhood cancer registry	Whole country 7.8 M	95 %	1976–2010	0–15
UK	National UK registry of childhood tumours	Whole country (Great Britain 1971–1992, UK 1993–2008) 58.5 M	>95 %	1971–2008	0–14

France and age ranges vary from 0–14 to 0–21. Childhood cancer registries and two institutional registries use the International Classification of Childhood Cancer, third edition (ICCC-3) which is based on the International Classification of Diseases (ICD) for Oncology third edition (ICD-O-3) with codes 9470–9472, 9474, 9480 for medulloblastomas, code 9473 for PNETs, and codes 9380–2, 9384, 9400–9411, 9420–9460 for gliomas. The Danish cancer registry used ICD7 with code 937 for medulloblastoma and with code 933, 934, 935 for gliomas and ICD10 with codes C715 and C716 for medulloblastoma and C710, C711, D330, D430, and D432 for gliomas. In the German and Austrian childhood brain tumor trial offices every tumor type was clearly identified.

DS is indicated at registration in all childhood cancer registries, and in the two Italian institutional registries. In Denmark, as for a previous study [3], data from the Danish Cancer Registry were linked to the Danish cytogenetic registry which covers the whole country since 1968. In the German and Austrian registries, due to a particular interest in genetic conditions associated with brain tumors, syndromal diseases including DS are recorded at registration.

Study design and statistics

Each of the participating cancer registries provided the numbers of medulloblastomas and CNS-PNETs found in children for the period and age groups covered in their

registries. Medulloblastomas and CNS-PNETs were studied together since they are both malignant embryonal tumors occurring mainly in infancy and childhood. In order to check ascertainment of DS by the registries, low and high grade gliomas were also extracted, since these tumors are believed to occur at a similar frequency in children with DS as they do in the general population.

The observed number of children with medulloblastomas and CNS-PNETs among children with DS was compared to the number expected, based on the numbers seen in the general population, using methods previously described for neuroblastoma [11]. First we estimated the size of the DS population on the basis of DS prevalence at birth as indicated by the European registry of congenital anomalies[12] which provided a crude rate of 10.4 DS children per 10,000 live births (or one in 961.5 births) between the years 1990–1994. Since then, the live birth prevalence of DS appears to have decreased with widespread prenatal screening in France and Denmark [13, 14], but there is little evidence that it has decreased in most other countries that contributed data to the present study, largely because of a countervailing increase in average maternal age [15–18]. Moreover, DS prevalence in Argentina may be somewhat higher than in Europe, Australia and Canada [19]. Life expectancy for children with DS has increased, with 95 % surviving 1 year from birth and 85 % alive at age 10 in some countries [16, 20, 21], though the 1-year survival rate for DS children born in South America in 1988–1992 was only 74 % [22]. Therefore, we used the birth rate for DS used in Satgé et al. [11] and estimated the number of DS children still alive as 85 % × 10.4/10,000 = 0.0884 % of the general child population.

The number of children with DS among the total number in each tumor category (medulloblastoma, CNS-PNET and glioma) was treated as a Poisson variable with 0.000884 times the number of tumor cases in that category. Statistical significance of the observed number of cases with DS was assessed by calculating the one-sided probability of observing at most that number of cases.

Results

Across the 13 countries studied, a total of 8,043 patients with malignant embryonal CNS tumors were identified, comprising 6,882 medulloblastomas and 1,161 CNS-PNETs (Table 2). Only one of these patients had DS, a 4-year-old boy with full trisomy 21 and cerebellar medulloblastoma whose case has been recently reported [23]. We calculated that 6.08 patients with medulloblastomas alone and 7.11 with medulloblastomas or CNS-PNETs were expected to have DS if the frequency of these tumors in DS were the same as in the general population. The probability of observing no more than one case of DS associated with medulloblastoma alone was 0.016. The probability of observing no more than one case of DS associated with medulloblastoma or CNS-PNET was 0.0066.

A total of 13,797 gliomas in nine countries (Table 2) were identified. Among these patients, 10 children with DS aged between 4 and 13 years (Table 3) were found. Using

Table 2 Medulloblastomas, central nervous system primitive neurectodermal tumours, and gliomas harvested in childhood cancer registries, institutional registries, and brain tumour registries from 13 countries, and their association with Down syndrome

Country	MBs and cPNETs Total	MBs + cPNETs	MBs and cPNETs in DS	Gliomas[a] Total	Gliomas in DS
Argentina	415	(377 + 38)	0	528	0
Australia	576	(409 + 167)	0	1,247	1
Austria	124	(103 + 21)	1[b]	NA	NA
Canada	338	(304 + 34)	0	NA	NA
Denmark	408	(408[c])	0	573	0
France	641	(533 + 108)	0	1,851	1
Germany	1,146	(963 + 183)	0	NA	NA
Hungary	400	(333 + 67)	0	884	1
Italy 1	330	(295 + 35)	0	561	1
Italy 2	117	(102 + 15)	0	314	0
Japan	605	(560 + 45)	0	NA	NA
Spain 1	124	(109 + 15)	0	325	0
Spain 2	90	(85 + 5)	0	196	0
Switzerland	256	(207 + 49)	0	413	0
UK	2,473	(2,094 + 379)	0	6,905	6
	8,043	6,882 + 1,161	1	13,797	10

MBs medulloblastomas, *cPNETs* central nervous system primitive neurectodermal tumours, *DS* Down syndrome, *NA* not available

[a] Low grade gliomas and high grade gliomas

[b] A medulloblastoma also reported separately (Benesch et al. [23])

[c] Only medulloblastomas, cPNETs not included

Table 3 Ten children with Down syndrome found among 13,797 low grade gliomas and high grade gliomas registered in nine countries

Country	Age (years) sex	Tumour histology	Location
UK	5 M	Astrocytoma	3rd ventricle
UK	8 F	Xanthoastrocytoma	Temporal region
UK	9 M	Astrocytoma	Occipital region
UK	4 F	Glioma	Brain stem
UK	8 M	Glioma	Brain stem
UK	4 M	Gliomatosis cerebri	Corpus callosum
France	10 F	Pilocytic astrocytoma	4th ventricle
Hungary	10 M	Glioma	Pons
Italy	8 F	Anaplastic astrocytoma	Thalamus
Australia	13 M	Astrocytoma	4th ventricle

the same calculation as for medulloblastomas and CNS-PNETs we calculated that 12.2 children with DS would be expected if the frequency of gliomas in DS is the same as in the general population.

Discussion

This is the largest epidemiological study to date on the occurrence of brain tumors in patients with DS. We were able to analyse a series of more than 8,000 medulloblastomas and central PNETs from ten nation-wide cancer registries or clinical/pathological-based registrations and five regional registries or clinical/pathological registrations spread over a total of 13 countries in four continents. For rare cancers and rare genetic conditions, collaborations of this kind are crucial to a better understanding of biological associations since they allow us to accumulate sufficient data from which to draw inferences. Although population based cancer registries may miss some cases, they are the best source available to conduct such studies. Another strength of this study is that the sources were the same for studied tumors and for tumors used as controls. The rarity of medulloblastoma, in the face of an incidence of gliomas not different from the non-DS population, suggests a specific impact of a supernumerary chromosome 21 in reducing neural cell embryonal tumors since neuroblastomas are also rare in DS [24].

Medulloblastomas which occur in the cerebellum, and CNS-PNETs which have a supratentorial location are histologically similar embryonal brain tumors. Together they >account for nearly 20 % of CNS tumors in children [9, 25, 26]. In the 1993 WHO classification of CNS tumors medulloblastomas are listed under the heading "PNETs", on the conceptual basis that medulloblastomas and PNETs share common progenitor cells in the subependymal matrix layer, and that their neoplastic transformation leads to tumors with similar morphological features and biological behaviour [27]. However, this concept has been challenged since medulloblastomas and CNS-PNETs do not bear the same genetic and cytogenetic anomalies [28, 29], and in subsequent WHO classifications medulloblastomas stand as an entity distinct from supratentorial PNETs [9]. Nonetheless, medulloblastomas and CNS-PNETs share a predominant neural differentiation, similar histological aspects and an almost identical age of onset with a peak at 7 years for medulloblastomas [7] and 5.5 years for CNS-PNETs [8]. Since these two groups of tumors are embryonal neoplasms, show mainly a neural differentiation, and have largely been studied together [30] we chose to include both of them in this study for conceptual and practical reasons.

There is growing evidence that medulloblastoma consists of four to five genetically different entities [31]. Little is known about the etiology of medulloblastomas and CNS-PNETs. Regarding exogenous agents, it has been suggested that the use of multivitamin supplements, and high dietary folate and vitamin C intakes from food during pregnancy decrease the risk of medulloblastomas and CNS-PNETs in the offspring [30]. An excess of medulloblastomas has been reported in rare genetic conditions such as Gorlin syndrome (basal cell nevus syndrome) [32] which is linked to an alteration of the Hedgehog signalling pathway, including germline mutations in the *SUFU* gene. An excess of medulloblastomas has also been observed in patients with Turcot syndrome in which colon polyps and brain tumors are associated in a context of alterations of the Wnt pathway. Similarly, an excess is seen in patients with Nijmegen syndrome as a result of defects in DNA repair signalling. These genetic associations helped to better understand mechanisms contributing to the mechanism of oncogenesis in medulloblastomas [33]. As some of these associations are extremely rare, they can only account for a minority of cases of medulloblastoma. The observation of a decreased frequency of medulloblastomas and CNS-PNETs in DS presents an opportunity for further study into the genetic and/or biological mechanisms involved in the genesis of these embryonal tumors.

In search of a protective mechanism

Searching for a mechanism involved in the reduction of incidence of medulloblastomas and CNS-PNETs in children with DS must take into account that gliomas are not less frequent and that intracranial germ cell tumors [34] are more frequent in DS compared to the general population.

These observations and the rarity of neuroblastoma in children with DS [24] strongly support the idea of a mechanism applying specifically to embryonal neural tumors. Deregulations of similar signalling pathways in medulloblastomas and neuroblastoma have been underlined [35]. Additionally, it has been demonstrated that the introduction of a supernumerary human chromosome 21 in pluripotent mouse embryonic stem cells injected in mouse lead to teratomas with a three fold lower percentage of neuroectodermal tissue compared to control embryonic stem cells derived teratomas [36].

As the decreased frequency of solid tumors in children and adults with DS is now well recognized, the possible mechanisms of this natural reduction in specific cancer types are being actively researched. The basic principle is that genes triplicated due to the supernumerary 21 chromosome interact with fundamental pathways involved in neoplastic transformation and progression, leading to some kind of resistance against solid tumors. This has encouraged the search for a single basic mechanism, such as an antiangiogenic effect, that would apply to a correspondingly wide range of tumors [37]. Since brain tumors, particularly gliomas are among the most angiogenic of human solid tumors [38], a decrease of brain tumors and specifically glial tumors should be observed in a condition such as DS in which antiangiogenic factors are overexpressed. However, glial tumors do not seem to occur less frequently in patients with DS, and cerebral germ cell tumors, like germ cell tumors of other sites [2] are even in excess compared with the general population.

The great amount of research conducted on the DS brain in recent decades in order to unveil the mechanisms of intellectual impairment has provided abundant data on anatomical, histological, physiological and molecular clues on the biological state of trisomy 21 neurons and glial cells. Importantly, it has been established that individuals with DS have a small hypocellular cerebellum with reduction of neurons in the granule layer [39]. This reduction caused by an inability to proliferate is linked to a reduced mitogenic response of granule cells precursors to Hedgehog protein signalling [40]. However, as the cellular density of granule cell neurons is reduced in DS to only 70 % of that in non-DS persons [39], this mechanism alone cannot explain the nearly seven fold decreased risk of medulloblastoma in children with DS. This suggests the presence of an as yet undiscovered potent biological mechanism inhibiting the neoplastic process in neural cells.

Since at least some of the different medulloblastoma entities are thought to originate from cerebellar granule neuron precursors in which the Shh pathway is overactivated [7], the reduced mitogene response in DS children could explain their resistance to medulloblastomas. It is possible that the over-expression of certain differentiation genes involved in neural differentiation in the cerebellum in DS such as *S100B*, *PCP4* and *DYRK1A* [24, 41] may account for the impaired response of cerebellar granule neuron precursors to Shh stimulation, since cell-cycle exit is intimately linked to differentiation programming [35].

This study has some limitations. First, the sources of data are heterogeneous, covering different time periods and age groups. Some sources are population-based cancer registries, while others are clinical or pathological tumor registries. Underreporting of cancer cases is possible, especially in the earlier years and in certain registries as noted in Table 1, but there is no reason to suppose that this would be biased with regard to DS status. If there are real variations in tumour incidence between the populations covered, the analysis assumes that differences in the effects of underlying risk factors apply proportionally without regard to DS status. In the absence of evidence to the contrary, we believe this is a reasonable assumption. In fact, the incidence of medulloblastoma/PNET appears to be remarkably constant, at least across European regions. In the multi-national ACCIS project, which used uniformly coded and validated data from population-based cancer registries, the age-standardised rate for these tumours in children under 15 years of age ranged only from 6.0 per million in Southern Europe to 6.9 per million in Eastern Europe [42]. Another possible source of error could be underreporting of DS, but this seems unlikely since DS is a frequent, well known, and usually easily recognizable genetic condition. Furthermore, pediatric oncological teams are used to treating children with DS suffering from leukemia. The fact that the observed number of cases of DS reported among children with gliomas was close to the expected number also suggests that children with DS were well reported. Diagnostic practices and classification for childhood CNS tumors have changed over the years and it is plausible that some of the cases of glioma listed in Table 3 would have been given a different diagnosis if they had presented more recently, but this would also be true for non-DS cases. From the combinations of tumor type and primary site it seems unlikely that any of these tumors was in fact a medulloblastoma. It is perhaps a little more likely that one of the supratentorial tumors could in fact have been a PNET, but the probability of observing no more than two cases of DS among the children with medulloblastoma or PNET based on 7.11 expected would still be only 0.0273, so the conclusion that there is a deficit of these tumor types in DS would still be reasonable. Accurate information was not available on the number and age distribution of children with DS over the study period and regions. The method of analysis does not assume, however, that prevalence of DS was the same across all regions and periods, only that the prevalence

estimate we used was a good approximation to the average across regions and periods. Because the method of calculation effectively assumes that all children with DS who die do not survive beyond infancy, the proportion of the total child population with DS and hence the expected numbers of tumors associated with DS are more likely to be underestimates than overestimates. Consequently, the tests for significantly low numbers of cases will tend to be conservative.

In conclusion, this study is the largest epidemiological study on primary brain tumors in persons with DS and the first to focus on embryonal brain tumors. It confirms that tumors of similar histogenesis, neuroblastoma and medulloblastoma, have an extremely low frequency in DS. This suggests that an unidentified biological mechanism linked to a supernumerary chromosome 21 mitigates the neoplastic transformation of neural cells into neuroblastoma and medulloblastoma.

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Conflict of interest All authors declare no conflict of interest.

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