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Low occurrence of familial neuroblastomas and ganglioneuromas in five consecutive GPOH neuroblastoma treatment studies

Alexander Claviez [a,*], Max Lakomek [b], Jörg Ritter [c], Meinolf Suttorp [d], Bernhard Kremens [e], Roswitha Dickerhoff [f], Dieter Harms [g], Frank Berthold [h], Barbara Hero [h]

[a] *Department of Paediatrics, University of Kiel, Schwanenweg 20, 24105 Kiel, Germany*
[b] *Department of Paediatrics, University of Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany*
[c] *Department of Paediatrics, University of Münster, Albert-Schweitzer-Str. 33, 48149 Münster, Germany*
[d] *Department of Paediatrics, University of Dresden, Fetscherstr. 74, 01307 Dresden, Germany*
[e] *Department of Paediatrics, University of Essen, Hufelandstr. 55, 45122 Essen, Germany*
[f] *Asklepios Children's Hospital, St. Augustin, Arnold-Janssen-Str. 29, 53757 Sankt Augustin, Germany*
[g] *Kiel Pediatric Tumour Registry, University of Kiel, Michaelisstr. 11, 24105 Kiel, Germany*
[h] *Department of Paediatrics, University of Köln, Josef-Stelzmann-Str. 9, 50924 Köln, Germany*

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Abstract

Familial neuroblastoma is of special interest in view of the oncogenesis of this tumour with its early manifestation in childhood. The inheritance seems to follow an autosomal-dominant Mendelian trait with incomplete penetrance. Familial neuroblastomas and ganglioneuromas have not been reported in detail within large treatment studies. A retrospective clinicopathological survey of patients reported to the German neuroblastoma treatment studies over 24 years was performed. Among 2863 patients (2752 neuroblastomas, 111 ganglioneuromas) included in five consecutive trials, only 22 hereditary cases in ten families were observed. Neuroblastomas were found in 18 patients and ganglioneuromas in four, accounting for less than one percent of all cases. Six patients with neuroblastomas had localised disease, seven had stage 4, three had stage 4S, and stage was unknown in two patients. In four families, two generations were affected, with ganglioneuromas occurring in the parental generation in two families. Two families had three affected patients. Contrary to previous reports, age distribution and number of primary tumours in patients with familial tumours were not significantly different from patients with sporadic tumours. The outcome of both groups was comparable. These data confirm the low prevalence of familial neuroblastoma and may help in counselling the affected families.

Keywords: Familial neuroblastoma; Ganglioneuroma; Childhood; Prognosis

1. Introduction

Neuroblastoma, the most common extracranial solid tumour in children, is characterised by sporadic occurrence in the vast majority of cases and a wide clinical heterogeneity including spontaneous regression and complex molecular findings [1,2]. Diagnosis is made within the first five years of life in over 90% of cases, but these tumours have also been repeatedly described in adult patients. Neuroblastomas represent nearly 9% of childhood malignancies in Germany, with an incidence of 1.3 per 100 000 corresponding to 140 newly diagnosed patients per year [3]. Since 1979, these tumours are treated in risk-adapted prospective

* Corresponding author. Tel.: +49 431 597 1622; fax: +49 431 597 1816.
E-mail address: a.claviez@pediatrics.uni-kiel.de (A. Claviez).

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multicentre trials of the German Society of Paediatric Oncology and Haematology (GPOH).

Prognosis is largely dependent on clinical factors, such as stage and age, as well as histopathological and molecular findings, such as proliferation rate and grading, *MYCN* status, aberrations of chromosomes 1, 11, 14, 17, neurotrophin receptor (trk) status, ploidy and telomerase activity [1,4]. Treatment options vary according to the estimated risk from a 'watch-and-wait' strategy to aggressive high-dose chemotherapy regimens including autologous haematopoietic stem cell transplantation [5].

Familial transmission in neuroblastomas has been rarely described with only 23 families and 55 affected members reported up to 1986 [6]. In this series described in 1986, Kushner and co-workers reported two of their own patients together with the results of a detailed literature research. Since that time, more than sixty further patients have been reported in small series or as case reports and much has been learned about the clinical course of disease and its genetics [7,8]. The first documented report about two siblings with neuroblastoma was published in 1945. However, in two prior publications, neuroblastoma seemed the likely diagnosis, but histological analysis was not performed in these cases (reviewed in Kushner and colleagues). Familial cases of neuroblastoma have been characterised by occurrence at a young age and multiple primary tumours [6,9,10]. Inheritance is suspected to follow an autosomal-dominant Mendelian trait with incomplete penetrance. In hereditary, as well as in sporadic, neuroblastomas, an association with Hirschsprung's disease, neurofibromatosis type 1, total colonic aganglionosis and central hypoventilation (Ondine's curse) has been reported [11]. Based on their findings in retinoblastomas, Knudson and Strong hypothesised in 1972 that hereditary cases may account for 20–25% of all neuroblastomas and pheochromocytomas [9]. However, the prevalence in several published series, was much lower ranging from 0.8 to <6% [6,12,13].

The purpose of this study was to establish the prevalence of familial neuroblastoma in five consecutive German neuroblastoma treatment studies, to characterize the clinical course of the index patients and their affected family members and to compare these findings with reported cases from the literature.

2. Patients and methods

We performed a retrospective analysis of all patients with neuroblastomas diagnosed since the initiation of the first German multicentre treatment study, NB-79. All patients with familial neuroblastomas and ganglioneuromas reported to the study centre until the end of 2002 were included. More than 90% of patients with neuroblastoma during the study period and 99% of patients within the last decade had been treated within the GPOH neuroblastoma trials [3]. Although data from patients with ganglioneuromas has been reported to the trial office since 1979, a systematic registration was not started until 1995. Therefore, an incomplete recording of patients with ganglioneuromas has to be assumed. The report forms specifically asked for familial occurrence from the very beginning of the NB trials. Information about the affected patients was obtained from these reports, from the medical records sent to the study centre and was supplemented by additional information from the local hospitals. Prior reports concerning family members of registered study patients with neuroblastoma or ganglioneuromas were also included in this series, as far as this information was available. In two families, only scarce data on affected family members could be obtained.

Data from sporadic and familial cases were analysed and compared for clinical features and outcome. All participating centres were asked to send diagnostic material for a central pathology review in the Paediatric Tumour Registry located in Kiel. Thus, reference histology was available for approximately 85% of all patients with neuroblastoma or ganglioneuromas. In the most recent study (NB-97), this figure exceeded 95%. If available, molecular findings, e.g., *MYCN* status, were included in the analysis. In addition, a review of the literature was performed by a Pubmed™ search using the keywords; "familial" or "hereditary neuroblastoma" or "neuroblastic tumours".

Statistical analyses were performed using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables, respectively, as appropriate. Survival analyses were performed according to the method by Kaplan and Meier with the log-rank test for a comparison of the differences. All analyses were calculated on a PC using the Statistical Package for the Social Science (SPSS) software (SPSS Inc., version 11.5.1, Chicago, IL, USA).

3. Results

A total of 2863 patients (1531 male, 1332 female) with neuroblastic tumours diagnosed until the end of 2002, were included in this analysis. There were 2752 neuroblastomas (96%) and 111 ganglioneuromas (4%). In the cohort, we identified 22 patients with familial tumours (18 neuroblastomas, 4 ganglioneuromas) in 10 families. This accounts for less than 0.1% hereditary cases for neuroblastomas and 4% for the registered ganglioneuromas, respectively. Six affected family members with neuroblastoma have been treated outside of the trials. Altogether, there were 10 affected male and 12 female patients. Localisation of the hereditary tumours was as follows:

13 patients had retroperitoneal or adrenal tumours, thoracic sites were affected in three cases. No cases of multifocal tumours were observed. Localisation could not be clearly defined in two affected family members. In two families, three persons were affected and in eight families two persons had familial neural crest tumours. Family #10 is of particular interest, because two affected relatives from the father's as well as from the mother's side were identified. Two affected generations were present in four families, while in the remaining six families, only one generation was affected. Consanguinity was not reported in the families described here. More detailed information can be obtained from the patients' characteristics, as summarised in Table 1.

None of the patients presented here had neurofibromatosis, Hirschsprung's disease or Ondine's curse. However, two patients, had pre-existing Beckwith-Wiedemann syndrome and Sotos' syndrome, respectively. Multiple primary tumours, described as a characteristic feature in familial neuroblastomas by some groups, were not found in our series of patients with hereditary tumours, but in 1.4% of those with sporadic neuroblastoma [6,14,15].

Information on stage was available for 16 patients with familial neuroblastoma. Six patients (38%) had localised disease and ten patients (63%) had disseminated disease (stage 4: seven patients, stage 4S: three patients). The stage distribution between sporadic and familial neuroblastomas is depicted in Fig. 1. With respect to age (see also Fig. 2), there were no obvious differences between sporadic and familial neuroblastomas with stages 1–3 and 4S. Patients with familial neuroblastoma and stage 4 ($n = 7$) in our cohort seemed to be younger than those with sporadic disseminated tumours. However, due to small numbers, the difference was not statistically significant (median age 17.0 *vs.* 33.8 months, $P = 0.12$).

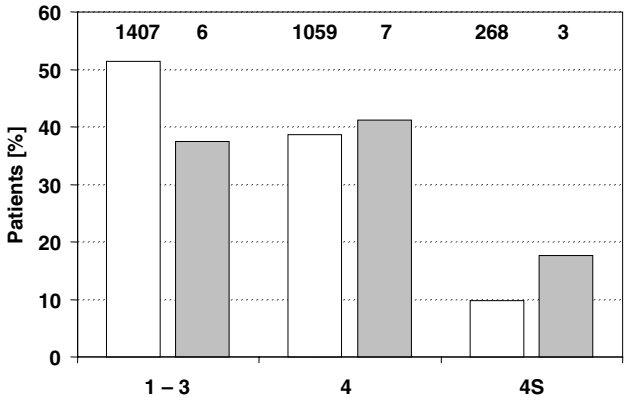

Fig. 1. Stage distribution in 2734 patients with sporadic (white columns) and 16 patients with familial (grey columns) neuroblastomas with available data. Ganglioneuromas were excluded.

Localised and disseminated diseases were identified among members of the same family (e.g., family #10). It is remarkable that in one family (#8), *MYCN* status was amplified in one patient (#8-1), but not in the other (#8-2), illustrating that different types of neuroblastoma can be found within the same family. Altogether, *MYCN* amplification was found in one of eight patients with familial neuroblastoma with available results and

Table 1
Clinical data for 22 patients with familial neuroblastomas and ganglioneuromas

UPN	Relation	Diagnosis	Gender	Stage	Age at diagnosis (months)	Multifocal tumour	*MYCN* status
1-1	Index	NB	M	4	6.1	No	ND
1-2	Mother	GN	F	–	120.1	No	ND
2-1	Index	NB	F	3	16.2	No	ND
2-2	Brother	NB	M	NA	NA	NA	ND
3-1	Index	NB	M	4S	3.5	No	Normal
3-2	Half-brother	NB	M	4	53.2	No	ND
4-1	Index	NB	M	4	12.5	No	ND
4-2	Sister	NB	F	2	14.3	No	ND
5-1	Index	NB	F	3	7.3	No	Normal
5-2	Cousin	GN	F	2	60.9	No	Normal
6-1	Index	NB	M	4S	2.3	No	ND
6-2	Sister	NB	F	NA	NA	NA	ND
6-3	Mother	GN	F	–	24.0	No	ND
7-1	Index	NB	F	3	24.7	No	Normal
7-2	Sister	NB	F	4	17.0	No	ND
8-1	Index	NB	F	4	62.2	No	Amplified (×40)
8-2	Niece	NB	F	2	7.4	No	Normal
9-1	Index	NB	M	1	49.0	No	Normal
9-2	Brother	GN	M	-	197.3	No	ND
10-1	Index	NB	M	4S	3.2	No	ND
10-2	Cousin	NB	M	4	20.3	No	Normal
10-3	Aunt	NB	F	4	9.1	No	ND

Abbreviations: F, female; GN, ganglioneuroma; M, male; NA, not applicable; NB, neuroblastoma; ND, not done; UPN, unique patient number.

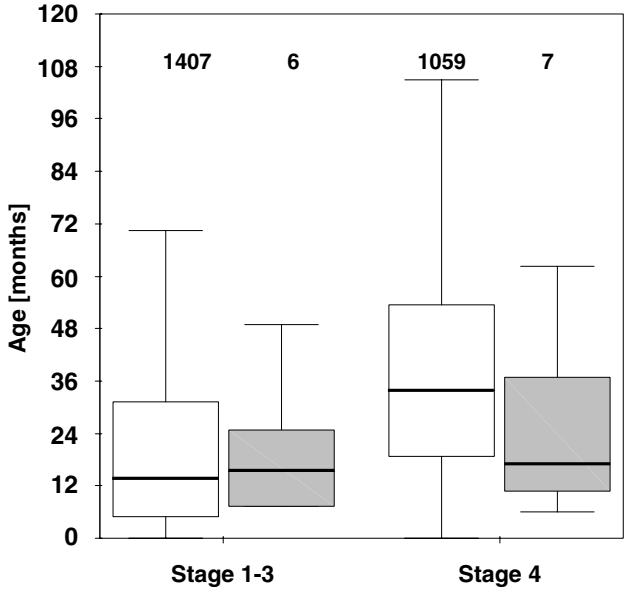

Fig. 2. Age at diagnosis in months of 2466 sporadic (white boxes) and 13 familial (grey boxes) neuroblastoma patients with data available on age and disease stage, depicted as box plots without extremes and outliers (Mann–Whitney test, stage 1–3: $P = 0.63$; stage 4: $P = 0.12$). Patients with stage 4S tumours and ganglioneuromas were excluded.

in 301 of 1797 patients (17%) with sporadic tumours. Moreover, we did not observe a different histopathological pattern in familial neuroblastic tumours compared with sporadic cases.

The median follow-up for the surviving patients is 5.9 years (range: 0–23.5 years). The probability for overall survival (OS) at 5 years for all patients with neuroblastoma is 66% ± 1%. The corresponding event-free survival (EFS) rate for these patients is 58% ± 1%. None of the 111 patients with ganglioneuromas had an event or died, including all four patients with familial ganglioneuroma. At the time of last contact, 10 of 18 patients (56%) with familial neuroblastoma were alive and eight have died. The causes of death were related to the tumour in seven patients and to the treatment in one patient. Four patients were lost to follow-up. One patient (#4-1) developed a meningeoma 16 years after radiotherapy for central nervous system (CNS) involvement and was treated by surgery. However, the follow-up line for this patient, is only two years.

4. Discussion

In this report analysis data from five consecutive neuroblastoma treatment studies including more than 2800 patients with neuroblastoma and ganglioneuroma, a total of 22 affected patients with familial tumours from ten families could be identified. Our figures point to a low familial occurrence of hereditary tumours. A recent report from France confirmed this low incidence. In the French series of 426 patients with neuroblastoma treated in the Institute Gustave Roussy over a 50-year period, a second case of neuroblastoma was observed in only five families (1%) [13]. Carlsen reviewed the Danish registries and reported two siblings among 246 patients with neuroblastomas (0.8%) between 1943 and 1980 [12]. Kushner concluded that for most patients with neuroblastoma, the risk of neuroblastoma in the subsequent generations appears to be less than 6% [6]. These numbers are far below the proposed frequency of 20–25% estimated by Knudson and Strong for neuroblastomas and pheochromocytomas, as derived from their figures on retinoblastomas 30 years ago [9].

A comprehensive report on the clinical course of familial neuroblastoma was published 17 years ago summing up 55 cases from 23 families with hereditary neuroblastomas [6]. By adding several case reports not included in that series [15–20], unpublished cases (two siblings from Austria; Christian Urban, Department of Pediatrics and Adolescence Medicine, University of Graz, Austria) and those reports published since the report by Kushner [7,21–26] together with the 10 families from our series, the total group expands to at least 146 patients from 62 families. Detailed information is not available from all of the reports, especially not from the epidemiological studies [8,27–29]. Moreover, as some families have been used for the identification of different molecular markers responsible for familial neuroblastoma, the same patients may have been reported in different publications [7,22,28,30,31]. Maris and co-workers [28] stressed the clinical heterogeneity of familial neuroblastoma even within the same family, a finding which is supported by our study. In addition, we did not observe histopathological differences between sporadic and familial neuroblastomas. In agreement with the analysis of Kushner and colleagues [6], we found no differences in the survival data between hereditary and sporadic tumours. Because of the low incidence of familial neuroblastomas, it is difficult to draw firm prognostic conclusions with respect to clinical outcome.

Multifocal tumours have been reported as a striking feature of familial neuroblastomas in several publications [6,7,15,32]. However, this finding, did not emerge in our series. Younger age in familial neuroblastomas has also been highlighted in several studies [6,9]. We were not able to confirm this observation for patients with localised disease. By contrast, the median age of patients with familial neuroblastomas with stage 4 was younger than in the sporadic cases (17.0 *vs.* 33.8 months), but this finding was not statistically significant (see also Fig. 2) and should be viewed with reservation due to the small numbers involved.

In our series, we did not observe an association of familial neuroblastoma with Hirschsprung's disease, Ondine's curse or neurofibromatosis, a feature, that

has been reported by several authors. However, two patients in the present report, had other accompanying diseases. Sotos' syndrome was observed in one patient (#10-2), a condition that has rarely been observed in neuroblastoma patients [33]. In another patient (#8-2), Beckwith-Wiedemann syndrome was observed and has a well known association with neuroblastoma [34].

MYCN status could be analysed in only a subset of patients, as it was not routinely performed in the earlier trials. The results obtained for *MYCN* status in familial tumours are also comparable to the group with sporadic tumours (one of eight *vs.* 301 of 1797). Thus, a separate subgroup according to *MYCN* status could not be defined.

Although the pattern of familial neuroblastoma is suspected to follow an autosomal-dominant trait with variable penetrance in some families [10,35,36], most familial cases that have been identified have occurred in one generation. Heredity was observed mainly among siblings, followed by half siblings or cousins. Five families with concordant twins have been described in detail [37–41]. Discordant twins have also been reported and seem to outweigh the concordant cases [42]. No cases of twins with familial neuroblastomas were observed in our series and in the smaller French and Danish series [12,13]. Only few families were reported to show tumour occurrence in parents and their children [12,14,21,36,43–45]. Except for a few cases, the affected parents had ganglioneuromas. Arenson published for the first time the occurrence of a neuroblastoma in the parental generation [43]. In our series, in two of four families with more than one generation of familial neuroblastoma, the mothers (#1-2, #6-3) had suffered from a previous ganglioneuroma detected at the age of twelve and two years, respectively.

The actual number of familial neuroblastomas might, however, be even higher for several reasons: in the early studies, as determined by autopsies for various reasons, neuroblastomas have been found in up to 1:200 of foetuses [46]. Moreover, a reduced penetrance of familial neuroblastomas due to spontaneous clinical or occult regression may be possible, thus these cases escapes detection. Maturation of neuroblastoma into ganglioneuroma might also result in an underestimation of the actual frequency. In addition, the condition may be lethal prior to reproductive ages [11].

Researchers have looked for a specific gene locus that is linked with familial neuroblastomas. Using different polymorphic markers, chromosome 1p36 was excluded as the responsible locus. *MYCN* amplification and loss of heterozygosity (LOH) of chromosome 1p in hereditary tumours did not differ from sporadic neuroblastomas [11]. Extensive analyses have not provided any evidence that RET (10q11) and EDNRB (13q22), two susceptibility genes that play a role in the pathogenesis of Hirschsprung's disease, are involved in the pathogenesis of sporadic and familial neuroblastomas [28]. By contrast, Tonini and colleagues [25] found deletion of 1p and paternal imprinting in two affected families. Recent work suggests that possibly more than one tumour suppressor gene may be involved in the multistep oncogenic development of this tumour. In another study from the University of Pennsylvania, genetic losses were detected in chromosomal regions 3p24-pter, 10p12-p13, 10q25-qter, 16q12-q22 and 20q13.3-qter [30]. More recently, the same group have published evidence from linkage analyses for a hereditary neuroblastoma predisposition locus, *HNB1*, on chromosome 16p12-13 [7]. The authors also found a strong correlation between LOH on chromosome 11q and LOH on chromosome 16p12-13, a finding with still undetermined significance. Besides 16p12-13, further loci for a predisposition to familial neuroblastomas may exist.

In conclusion, this survey defines the risk of developing familial neuroblastoma to be less than 1%, a result that is in line with other reports. In addition, from our experience, the clinical behaviour of sporadic and familial tumours do not seem to be different. *Multifocal* primary tumours and early manifestation were not associated with familial neuroblastoma or ganglioneuromas in this study. For effective genetic counselling, a reliable molecular marker for familial neuroblastomas needs to be identified.

Conflict of Interest Statement

The authors declare that they have no financial or personal relationships to declare.

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