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Histological concordance in familial central nervous system tumors: Evidence from nationwide Swedish Family-Cancer Database

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ABSTRACT

Background: Published studies have shown that familial risks in the primary central nervous system (CNS) tumors are usually histology-specific. If genetic factors indeed determine tumor histology it would be expected that histological types would agree between affected first-degree relatives (FDRs).
Material and methods: This study was conducted using the nationwide Swedish Family-Cancer Database. FDR pairs were defined where both of them had the same histological subtype of CNS tumor. The histological concordance was determined using kappa agreement test.
Results: We identified 858 familial patients (333 parent–offspring pairs, 97 sibling pairs) with primary CNS tumors. Proportion of spinal hemangioblastoma out of all familial hemangioblastomas (21%) was significantly higher than that in sporadic patients (7%; $P = 0.001$). The highest kappa value was found for hemangioblastoma among parent–child pairs (kappa = 86%, 95% CI: 74–98%). There was a moderate agreement for concordant neurinoma among father–daughter pairs (kappa = 48% 95% CI: 15–81%). Low grade glioma showed significant agreement among mother–daughter (kappa = 33%, 95% CI: 9–57%) and father–daughter pairs (kappa = 39%, 95% CI: 11–67%), but not in mother–son (kappa = 10%, 95% CI: −13% to 32%) and father–son pairs (kappa = 9%, 95% CI: −1% to 40%). There was histological agreements for meningioma in mother–offspring (kappa range = 20–27%) but not in father–daughter (kappa = 14%, 95% CI: −8% to 35%) and father–son pairs (kappa = 9%, 95% CI: −12% to 30%).
Conclusions: Our findings suggest that shared genetic risk factors between family members could lead to specific histological types in the familial CNS tumors, especially in hemangioblastoma and neurinoma. Our data may also suggest interactions between sex hormone and some genes contributing to familial meningioma and low grade glioma.

1. Introduction

Primary tumors of the central nervous system (CNS) comprise various histological subtypes with a vast range of molecular differentiations, location of tumor, age at onset, degree of malignancy, and prognosis [1,2]. Based on the Central Brain Tumor Registry of the United States, meningioma, and gliomas constitute more than 60% of the histological subtypes of primary CNS tumors [3]. A vast majority of brain tumors (BT) are sporadic, occurring without underlying familial disorder [4]. Overall few environmental factors are known to predispose to CNS tumors at the population level and, consistently, there is no correlation of risk for these tumors among spouses [5,6]. The familial aggregation has been reported solely in about 5% of BTs, especially for gliomas [4,6]. On the other hand, a strong association exists between the CNS malignancies in several well-characterized inherited syndromes, including Li–Fraumeni syndrome (LFS), neurofibromatosis (NF) types 1 and 2, tuberous sclerosis and von Hippel–Lindau (VHL) diseases [4,7]. However, these syndromes, caused by rare inherited mutations, explain probably only 1–2% of patients with the CNS tumors [8].

Epidemiological studies on familial cancer provide the scientific basis for clinical counseling and guide clinicians in therapeutic decisions [9]. Therefore, despite the fact that the

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positive familial history as a risk factor can explain only a small proportion of BTs, there is a continued need to conduct studies on familial aggregation and on histological concordance among familial CNS tumors. The first debates on familial aggregation of the CNS tumors emerged during the 1960s with a focus to brain gliomas [10,11]. Subsequent case-control and cohort studies revealed familial clustering of astrocytoma, meningioma, and medulloblastoma [12,13]. In our previous studies we have already shown that offspring of parents with meningioma and astrocytoma have a higher risk for developing the same histological subtypes compared to those without such a family history [14].

Ultimately, these observational approaches toward attributed familial clustering of BT would lead to experimental studies on the main underlying causes of the genetic alterations leading to CNS tumors [15]. In the published studies, familial risks in primary CNS tumors are highest for concordant histological types suggesting that genetic factors promote histology-specific tumors [6,14,16]. Therefore, seeking for histological agreements in family clusters would be a logical way for addressing the genetic predisposition to specific histological subtypes [17]. The main problem with these kinds of studies is that they generally require a large numbers of familial cases with histologically confirmed tumors, which are rarely available [16]. In this study, using the world's largest family database, the nationwide Swedish Family-Cancer Database (FCD), we assessed histological concordance among the first-degree relative (FDR) pairs with familial brain and spinal tumors.

2. Material and methods

This study was conducted using the latest version of the FCD, FCD2010 which contains individuals born in Sweden from 1932 to 2010 (offspring generation) with their biological parents plus immigrants (parent generation). The FCD includes population-based data from the Multigeneration Registry, national censuses (1960, 1970, 1980, and 1990), the Swedish Cancer Registry and death notifications (cause of death register) [18]. The completeness of data has been reported to be near 100% with more than 1.7 million registered first primary invasive cancers and possibility to analyze cancer occurrence over three generations [18,19].

In the FCD, first-degree relative (biological parent–child and sibling–sibling) pairs with concordant histological types of CNS tumors were defined. A 4-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) has been used in the FCD since 1958 to define the topography (primary site) of tumors. The code 193.0 was used for BT and the code 193.1 for spinal tumors; the peripheral nerve tumors (code 193.3) were excluded from this study. We used pathology-anatomy diagnosis (PAD) codes (WHO/HS/CANC/24.1) to determine the histological subtypes of the CNS tumors including glioma (pathology codes 471, 475, and 476), medulloblastoma (436), neurinoma (451 and 456), ependymoma (481, 485, and 486), meningioma (461 and 466), and hemangioblastoma (501 and 511). Patients with possible VHL identified based on presence of brain/spinal hemangioblastoma accompanied with renal cell carcinoma of kidney, retinal hemangioblastoma, and pheochromocytoma [20].

For calculating the histological agreement of CNS tumors among FDR pairs, we used the unweighted kappa statistics with 95% confidence intervals (95% CI) [21,22]. The kappa coefficient, described by Cohen in 1960, is a standard tool for the analysis of chance corrected agreement on a binary outcome between two observers or two independent events [23–25]. The histological agreement calculated in FDR pairs with dichotomous variable in a two-by-two table for each histological subtype (e.g., meningioma in father yes/no versus meningioma in his child yes/no). According to the Landis and Koch scale, when kappa statistic is higher than 80% the agreement is almost perfect. By decreasing the level of agreement, the kappa value decreases, so that the kappa between 61% and 80% means the agreement is substantial; 41–60% moderate; 21–40% fair; 1–20% slight; and zero indicates that the agreement is limited to what would be expected by chance alone [26]. The minimum possible kappa value is −100%, corresponding to a complete disagreement. Kappa coefficient and the 95% CI were calculated using Fleiss methods in the SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA) [27]. The Lund University Regional Ethics Committee in Sweden has approved the study protocol.

3. Results

In the FCD, there were 47,105 sporadic patients with the primary CNS tumors and 1021 familial cases (containing 1.6–5.8% of CNS tumors; Table 1). Apart from peripheral nerve tumors, in both familial and sporadic cases 93–94% of tumors occurred in the brain and the rest occurred in the spinal cord. The most common spinal tumors in familial and sporadic patients were ependymomas and neurinomas. Occurrence of familial hemangioblastoma in spinal cord (21%) was significantly higher than sporadic hemangioblastoma (7%; $P = 0.001$). According to our data familial CNS tumor significantly occur in younger ages (mean age = 42.9 years) in comparison with sporadic (mean age = 55.3) patients ($P < 0.001$). Further information on sex and age differences and spouse correlation has been provided in the online-only supplementary materials (Table S1 in online supplementary material).

The main histological groups of the CNS tumors (defined by PAD codes) were gliomas [including its low grade, World Health Organization (WHO) grades I and II, and high grade, WHO grades III and IV, subtypes], meningioma, hemangioblastoma, neurinoma, medulloblastoma and ependymoma. After excluding ill-defined and very rare specified histology reports, there remained 858 familial cases with the CNS tumors and ultimately we could identify 430 FDR pairs (333 parent–offspring pairs and 97 sibling pairs).

Out of 430 FDR pairs, glioma with 130 pairs showed the most common familial clustering and medulloblastoma (two FDR pairs) and ependymoma (one FDR pair) had the lowest clustering (Table 2). According to these data, hemangioblastoma showed the highest kappa value representing an almost perfect agreement among FDR pairs (kappa = 84%), for parent–offspring (kappa = 86%) and sibling pairs (kappa = 81%) which were considerably higher than those of other histological subtypes. Except for ependymoma and medulloblastoma, all other histological subtypes showed significant agreements in parent–offspring pairs. Among sibling pairs there were significant agreements only for hemangioblastoma, neurinoma and high grade glioma. Further stratification by sex and age of sibling pairs did not change the results substantially (data not shown).

Out of 858 patients with familial CNS tumors, we identified 22 patients with hemangioblastoma and with a possible VHL syndrome. When we excluded VHL patients, the kappa coefficient for hemangioblastoma decreased in all FDR pairs except for mother–son (kappa = 85%) and father–son pairs (kappa = 100%), yet the difference failed to reach statistical significance (Table 3). There were 192 mother–offspring and 141 father–offspring pairs in our dataset. Further stratification of low grade glioma histological subtype among parent–offspring pairs by sex of children showed a significant fair agreement among mother–daughter (kappa = 33%, 95% CI: 9–57%) and father–daughter pairs (kappa = 39%, 95% CI: 11–67%). However, we did not find significant agreement for this histology among mother–son and father–son pairs. On the other hand, high grade glioma showed a