Journal of Neuro-Oncology (2018) 138:271–281
https://doi.org/10.1007/s11060-018-2816-6

LABORATORY INVESTIGATION

Allergic conditions and risk of glioma and meningioma in the CERENAT case-control study

Camille Pouchieu[1] · Chantal Raherison[1,2] · Clément Piel[1] · Lucile Migault[1] · Camille Carles[1,3] · Pascale Fabbro-Perray[4,5] · Hugues Loiseau[6] · Jean-Sébastien Guillamo[7] · Pierre Lebailly[8,9] · Isabelle Baldi[1,3]

Received: 28 November 2017 / Accepted: 27 February 2018 / Published online: 2 March 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Inverse association between allergic conditions and glioma risk has been consistently reported in epidemiological studies with little attention paid to potential environmental confounders; the association with meningioma risk is less consistent. We examined the association between allergy history and risk of glioma and meningioma in adults using data from the CERENAT (CEREbral tumors: a NATional study) multicenter case-control study carried out in 4 areas in France in 2004–2010. Participants' histories of doctor-diagnosed allergic asthma, eczema, rhinitis/hay fever and other allergic conditions were collected at onset through a detailed questionnaire delivered in a face-to-face interview. Conditional logistic regression for matched sets was adjusted for participants' educational level and mobile phone use. A total of 273 glioma cases, 218 meningioma cases and 982 matched controls selected from the local electoral rolls were analyzed. A significant inverse association was found between glioma and a history of any allergy (OR 0.52, 95% CI 0.36–0.75), with a dose–effect relationship with the number of allergic conditions reported (p-trend = 0.001) and a particularly strong association with hay fever/allergic rhinitis (OR 0.46, 95% CI 0.30–0.72). Interestingly, associations with glioma risk were more pronounced in women. For meningioma, no association was observed with overall or specific allergic conditions. Our findings confirmed the inverse association between allergic conditions and glioma risk but questioned the role of allergy in meningioma risk. Future research is needed to clarify the biological mechanism of overall allergy and allergic rhinitis on glioma and to confirm the different effect by gender.

Keywords Allergy · Glioma · Meningioma · Primary central nervous system neoplasm · Case-control study

Introduction

Apart from ionizing radiation and rare genetic syndromes, the etiology of brain tumors is unknown [1]. Environmental risk factors such as pesticides [2–4], radiofrequency electromagnetic fields (RFs) via cell phone use [5, 6] or

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11060-018-2816-6) contains supplementary material, which is available to authorized users.

✉ Camille Pouchieu
camille.pouchieu@u-bordeaux.fr

1 Université de Bordeaux, INSERM, Bordeaux Population Health Research Center, Team EPICENE, UMR 1219, 146, rue Léo Saignat, 33076 Bordeaux Cedex, France

2 CHU de Bordeaux, Service de Pneumologie, 33076 Bordeaux Cedex, France

3 CHU de Bordeaux, Service de Médecine du Travail, 33076 Bordeaux Cedex, France

4 Unité de Biostatistiques Epidémiologie, Institut Universitaire de Recherche Clinique, Université de Montpellier I, 34093 Montpellier Cedex, France

5 BESPIM, CHU de Nîmes, 30029 Nîmes Cedex, France

6 CHU de Bordeaux, Service de Neurochirurgie A, 33076 Bordeaux Cedex, France

7 Département de Neurologie, CHU de Caen, Caen, France

8 INSERM, UMR 1086 ANTICIPE, Université de Caen Normandie, 14000 Caen, France

9 Centre de Lutte Contre le Cancer François Baclesse, 14076 Caen Cedex 05, France

dietary intake of nitroso compounds [7, 8] may increase the risk of brain tumors. Regarding intrinsic risk factors, increasing age, gender, body mass index [9, 10] and ethnicity [11] may play a role in the occurrence of brain tumors. Recently, a history of allergy, including eczema, asthma and/or hay fever has been consistently linked with a decreased risk of glioma in several epidemiological studies, mainly case-control studies, with different exposure assessment strategies [12–16]. The Glioma International Case-Control (GICC) study based on 4533 cases and 4171 controls from 14 study sites found that respiratory allergies, asthma and eczema were associated with a lower glioma risk of about 30% [12]. A meta-analysis based on 12 case-control studies and one cohort study concluded that there is a similar decrease in risk associated with eczema [14]. In addition, allergy-related biomarkers, such as the level of IgE [17, 18], allergy-related serum cytokines [19] and polymorphisms in allergy-related genes [20], whose measurement was unaffected by recall and reporting, were also found to be inversely associated with glioma risk.

The inverse association between allergic conditions and cancer risk was not restricted to the brain. A recent review of epidemiological studies on the relationship between site-specific cancers and atopy also suggested a protective effect of atopic diseases against pancreatic cancer and acute lymphoblastic leukemia [21]. Most studies on atopic diseases and non-Hodgkin lymphoma or colorectal cancer reported an inverse association but asthma has been observed to be a risk factor for lung cancer.

The link between the occurrence of meningioma and allergic conditions has been given much less attention and this has led to date to inconsistent results. In two previous meta-analyses based on five case-control and two cohort studies on allergy conditions and meningioma risk, no significant inverse association with allergy was found, except for eczema (OR 0.75; 95% CI:0.65–0.87) [15, 22]. Recently, a meta-analysis based on eight case-control studies and two cohorts found that allergic conditions, and specifically asthma and eczema, were associated with a decreased risk of about 20% [23].

However, there was substantial heterogeneity among study results, which could be explained by differences in potential confounders taken into account in individual studies. Notably, the role of environmental or occupational risk factors (RFs, pesticides) and lifestyle habits (smoking status, dietary habits and alcohol consumption) were little considered.

The aim of the CERENAT case-control study was to explore the associations between a medical history of allergy and the risk of glioma and meningioma, with detailed information on many potential lifestyle, occupational and environmental risk factors, including smoking status, alcohol consumption, dietary intake, exposure to RFs via mobile phone use and occupational exposure to pesticides.

Methods

Study population

CERENAT is a multicenter population-based case-control study initiated in 2004, designed to study the role of occupational and environmental factors in the etiology of primary brain tumors in adults. Details of the CERENAT study were described in a previous publication that explored the relationship between brain tumors and mobile phone use [24]. Eligible cases were all subjects aged 16 years and over (age limit between pediatric and adult medicine for healthcare services), with a benign or malignant central nervous system (CNS) tumor diagnosed between 2004 and 2010, and living in one of four French areas (Gironde, Calvados, Manche, Hérault) at diagnosis. Cases were identified with the collaboration of a network of practitioners involved in the diagnosis and therapeutic management of patients and, with the aim of being exhaustive, from population-based cancer registries. All diagnoses were established by either a neuropathological or, for cases with no histological diagnosis, a clinical and radiological assessment. Primary brain tumors with the following ICDO-3 topography codes were included: C70.0–C70.9, C71.0–C71.9 and C72.2–C72.9. Patients with recurrent tumors, metastases, pituitary tumors, genetic syndrome or AIDS were excluded. Cases were classified according to morphology codes as gliomas, meningiomas, acoustic neuromas, lymphomas and other unspecified primary brain tumors. In this analysis, only glioma and meningioma cases were considered.

For each case, two controls with no history of CNS tumor were randomly selected from the local electoral rolls during the period 2005–2008, individually matched on age (±2 years), sex and area of residence.

Data collection

Data were collected through standardized questionnaires delivered as face-to-face non-blinded structured interviews by trained interviewers. When cases were in a severe clinical condition or deceased, a proxy was invited to complete a simplified questionnaire, which was subsequently completed by their matched controls. The questionnaire covered sociodemographic characteristics, medical history, lifestyle (smoking, dietary and alcohol intake) and detailed occupational and environmental data. Dietary and alcohol data were collected using a food frequency questionnaire [25].

Allergic conditions were defined by a positive answer to the following questions: “Have you ever had an asthma

attack? (1st question), eczema? (2nd question), allergic rhinitis or hay fever? (3rd question), other allergic conditions?" (4th question). For each question, the subjects were asked if the allergic condition was diagnosed by a physician. When reporting other allergic conditions, subjects were asked about the type of allergy. Information on the age at first diagnosis of allergic conditions and treatment methods was not collected.

The role of potential confounders highlighted by previous studies was considered: educational level (primary school or less, secondary school, high school and university), smoking status (never, former or current smokers), occupational pesticide exposure (defined as having performed treatment tasks on crops, gardens, wood or other circumstances in any job during life). As significant positive association was found in the heaviest users of mobile phone and several associations was observed between CNS tumors and dietary and alcohol intakes in previous analyses of the CERENAT study, [24, 25] we also tested the potential confounding effect of alcohol consumption (classified as excessive in men drinking over three glasses per day and over two glasses per day in women), consumption of fruit, vegetables, grilled meat and poultry (according to the average frequency of consumption of specific food) and mobile phone use (heavy, moderate or no use). As several studies suggested that exposure to environmental farming in early childhood was associated with reduced atopy in adults [26], we also tested the role of living on a farm during the 1st year of life (yes or no).

Statistical analyses

The date of diagnosis was taken as the index date for each case and its two matched controls. We used conditional logistic regression to estimate adjusted ORs and 95% CIs testing the associations between a history of any doctor-diagnosed allergies (including asthma, eczema and/or hay fever/allergic rhinitis), specific allergic conditions (asthma, eczema, hay fever/allergic rhinitis and other type of allergies), the number of allergy conditions (excluding other type of allergies) and brain tumor risk. For each allergic condition, the reference category consisted of participants with no diagnosis of the condition considered. Separate analyses were conducted for gliomas and meningiomas. Potential confounders associated with gliomas or meningiomas in the univariate analyses ($p < 0.25$ for each covariate) were included in the multivariate analyses. As information on alcohol consumption was missing for 23% of gliomas and 5% for meningiomas, it was not included in the multivariate analyses. Thus, the multivariate models were adjusted for educational level and mobile phone use. As sex was a matching factor, we did not evaluate the possible effect modification by sex but we stratified analyses by sex. Interaction terms between allergy and educational level, mobile phone use and the fact of living on a farm during the first year of life, childhood and lifetime were entered into the conditional logistic regression model to assess potential effect modification.

To assess potential reporting bias, sensitivity analyses were conducted excluding proxy respondents. Additional adjustments for alcohol consumption, smoking status, occupational exposure to pesticides and the fact of living on a farm during the first year of life were also tested. For each allergic condition, complementary analyses were performed 1/by adjusting for other allergic conditions and 2/using subjects with no allergic condition at all as reference group.

Analyses were carried out using SAS software version 9.3 (SAS Institute, Cary, North Carolina, USA). All statistical tests were two-sided at an alpha level of 0.05.

Results

Characteristics of the population

Out of the eligible subjects (851 cases and 4579 controls), 95% of cases and 61% of controls were successfully contacted and a total of 596 cases (73%) and 1192 controls (45%) among those contacted were included in the CERENAT study. Participation rates were 66% for glioma cases and 75% for meningioma cases. The main reasons for non-participation were refusals (48%), severe condition or death (38%) or unreachable subjects (14%). After exclusion of non-glioma and non-meningioma CNS tumors ($n = 105$), 1473 subjects were included in the present analysis: 273 cases and 546 controls for gliomas; 218 cases and 436 controls for meningiomas. For each subtype (gliomas and meningiomas respectively), neuropathological assessment represented 96% of diagnoses, and clinical and radiological assessment represented 4%.

The main socio-demographic characteristics of overall CNS cancer cases and matched controls are presented in Table 1 and separately for the two subgroups of histological subtypes (gliomas and meningiomas) in Table 2. The average age was 56 years for gliomas and 61 years for meningiomas and men represented 58 and 24% of the population, respectively. The proportion of proxy interviews was 23% for gliomas and 5% for meningiomas. The level of education was higher in controls than in cases ($p = 0.03$ for glioma and $p = 0.02$ for meningioma). The proportion of alcohol consumers was significantly higher in controls ($p < 0.0001$ for glioma and $p = 0.0004$ for meningioma). Cases were more frequently heavy users of mobile phone than controls (10.2% vs. 5.9% for gliomas, $p = 0.04$; 6.8% vs. 2.9% for meningiomas, $p = 0.01$). Smoking status, occupational pesticide exposure and living on a farm in early childhood were not associated with either glioma or meningioma risk.

Table 1 Main characteristics of the overall CNS cancer cases and matched controls, CERENAT, 2004–2010

	N[a]	Cases (n = 596)		Controls (n = 1192)		OR (95% CI)	P[b]
		N	%	N	%		
Sex	1788						NA
Men		260	43.6	520	43.6	NA	
Women		520	56.4	672	56.4	NA	
Age (mean ± SD)[b]	1788	58.4	14.9	59.5	14.6	NA	NA
Simplified questionnaire	1788	95	15.9	190	15.9	NA	NA
Education	1785						< 0.0001
Primary school or less		153	25.8	243	20.4	1.00	
Secondary school		221	37.2	376	31.6	0.83 (0.62–1.12)	
High school		100	16.8	226	19.0	0.62 (0.44–0.87)	
University		120	20.2	346	29.0	0.48 (0.34–0.66)	
Smoking status	1781						0.6
Never smoker		285	48.1	586	49.3	1.00	
Former smoker		214	36.2	406	34.1	1.09 (0.86–1.39)	
Current smoker		93	15.7	197	16.6	0.96 (0.71–1.31)	
Alcohol[c]	1503						< 0.0001
No consumption		255	50.9	328	32.7	1.00	
Moderate consumption		205	40.9	550	54.9	0.45 (0.36–0.57)	
Excessive consumption		41	8.2	124	12.4	0.35 (0.23–0.53)	
Occupational pesticide exposure	1788						0.4
No		550	92.3	1113	93.4	1.00	
Yes		46	7.7	79	6.6	1.21 (0.80–1.81)	
Mobile phone use[d]	1699						0.002
No use		297	53.1	577	50.6	1.00	
Moderate use		213	38.1	504	44.2	0.81 (0.64–1.02)	
Heavy use		49	8.8	59	5.2	1.65 (1.05–2.59)	
Farm in early childhood	1724						0.7
No		453	79.6	909	78.7	1.00	
Yes		116	20.4	246	21.3	0.95 (0.73–1.22)	

NA not available

[a]Available data

[b]p value for log likelihood ratio test

[c]Only for detailed questionnaire respondents. Alcohol consumption was classified as excessive in men drinking over three glasses of wine, cider, beer or spirits per day, and over two glasses per day in women

[d]Moderate use: cumulative duration < 896 h during life; heavy use: cumulative duration ≥ 896

Prevalence of any allergy and specific allergic conditions

A total of 588 (33%) subjects reported a history of any allergy diagnosed by a physician. The most frequent allergic condition reported by the sample was hay fever/allergic rhinitis (21.4%), followed by eczema (14.7%) and asthma (8.2%) and 10.2% reported other types of allergy. Other allergies (n = 182) were mainly medication allergy (46%), unspecified allergy (44%) and the remaining 10% concerned food (n = 2), cosmetics (n = 3), chemicals (n = 4), metals (n = 5) and adhesives (n = 4). Including hay fever/allergic rhinitis, asthma and/or eczema, 7.4% reported two symptoms and 1.9% reported three symptoms. A history of any allergy was reported by 23.4% (37.8%) of glioma cases (controls), and 33.0% (33.3%) of meningioma cases (controls) (data not shown).

Gliomas

Adjusting for educational level and mobile phone use (Table 3), we observed a significant inverse association between a history of any allergy and risk of glioma (OR 0.52, 95%-CI 0.36–0.75) and there was a significant trend of risk with the number of conditions reported (p-trend = 0.001). For specific allergic conditions, we

Table 2 Main characteristics of the study population in the glioma and meningioma groups, CERENAT, 2004–2010

	Gliomas (N = 819)							Meningiomas (N = 654)						
	N[a]	Cases (n = 273)		Controls (n = 546)		OR (95% CI)	P[b]	N[a]	Cases (n = 218)		Controls (n = 436)		OR (95% CI)	P[b]
		N	%	N	%				N	%	N	%		
Sex	819						NA	654						NA
Men		158	57.9	316	57.9	NA			53	24.3	106	24.3	NA	
Women		115	42.1	230	42.1	NA			165	75.7	330	75.7	NA	
Age (mean ± SD)[b]	819	56.3	16.3	57.4	15.9	NA	NA	654	60.9	11.6	61.9	11.5	NA	NA
Simplified questionnaire	819	63	23.1	126	23.1	NA	NA	654	12	5.5	24	5.5	NA	NA
Education	818						0.03	654						0.02
Primary school or less		63	23.2	88	16.1	1.00			60	27.5	115	26.4	1.00	
Secondary school		97	35.6	173	31.7	0.67 (0.42–1.06)			86	39.4	129	29.6	1.24 (0.80–1.92)	
High school		53	19.5	112	20.5	0.55 (0.33–0.92)			37	17.0	81	18.6	0.84 (0.49–1.42)	
University		59	21.7	173	31.7	0.39 (0.23–0.65)			35	16.1	111	25.4	0.57 (0.34–0.98)	
Smoking status	814						0.3	654						0.1
Never smoker		111	41.1	250	46.0	1.00			118	54.2	238	54.6	1.00	
Former smoker		104	38.5	202	37.1	1.17 (0.82–1.67)			77	35.3	129	29.6	1.22 (0.81–1.83)	
Current smoker		55	20.4	92	16.9	1.36 (0.89–2.09)			23	10.6	69	15.8	0.65 (0.37–1.16)	
Alcohol[c]	630						< 0.0001	618						0.0004
No consumption		102	48.6	121	28.8	1.00			107	51.9	148	35.9	1.00	
Moderate consumption		89	42.4	238	56.7	0.41 (0.28–0.60)			84	40.8	219	53.2	0.51 (0.35–0.73)	
Excessive consumption		19	9.0	61	14.5	0.30 (0.16–0.56)			15	7.3	45	10.9	0.38 (0.19–0.76)	
Occupational pesticide exposure	819						0.07	654						0.9
No		244	89.4	507	92.8	1.00			208	95.4	415	95.2	1.00	
Yes		29	10.6	39	7.2	1.63 (0.95–2.79)			10	4.6	21	4.8	0.95 (0.43–2.09)	
Mobile phone use[d]	778						0.04	627						0.01
No use		115	45.3	239	45.6	1.00			131	63.6	243	57.7	1.00	
Moderate use		113	44.5	254	48.5	0.94 (0.66–1.34)			61	29.6	166	39.4	0.67 (0.45-1.00)	
Heavy use		26	10.2	31	5.9	2.05 (1.07–3.94)			14	6.8	12	2.9	2.04 (0.87–4.79)	
Farm in early childhood	784						0.8	636						0.4
No		205	78.8	418	79.8	1.00			171	81.4	332	77.9	1.00	
Yes		55	21.2	106	20.2	1.04 (0.72–1.52)			39	18.6	94	22.1	0.83 (0.53–1.27)	

NA not available;

[a]Available data

[b]p value for log likelihood ratio test

[c]Only for detailed questionnaire respondents. Alcohol consumption was classified as excessive in men drinking over three glasses of wine, cider, beer or spirits per day, and over two glasses per day in women

[d]Moderate use: cumulative duration < 896 h during life; Heavy use: cumulative duration ≥ 896

Table 3 Adjusted ORs (95% CIs) for glioma and meningioma in relation to a history of any allergy or specific allergic conditions, CERENAT, 2004–2010

	Gliomas				OR (95% CI)[a]	Meningiomas				OR (95% CI)[a]
	Cases (n = 253)		Controls (n = 524)			Cases (n = 206)		Controls (n = 421)		
	N	%	N	%		N	%	N	%	
Any allergy[b]										
No	189	75.9	319	62.2	1.00	138	68.0	275	66.4	1.00
Yes	60	24.1	194	37.8	0.52 (0.36–0.75)	65	32.0	139	33.6	0.87 (0.60–1.28)
Asthma[c]										
No	235	93.2	481	91.8	1.00	189	92.2	387	92.4	1.00
Yes	17	6.8	43	8.2	0.70 (0.37–1.32)	16	7.8	32	7.6	1.01 (0.53–1.91)
Eczema[d]										
No	224	88.5	440	84.6	1.00	178	87.2	350	83.7	1.00
Yes	29	11.5	80	15.4	0.72 (0.44–1.16)	26	12.8	68	16.3	0.66 (0.39–1.12)
Hay fever[e]										
No	215	86.7	379	73.9	1.00	164	80.4	331	79.8	1.00
Yes	33	13.3	134	26.1	0.46 (0.30–0.72)	40	19.6	84	20.2	0.92 (0.58–1.45)
Number of allergies										
0	189	76.5	319	62.7	1.00	138	68.6	275	66.9	1.00
1	42	17.0	137	26.9	0.54 (0.36–0.82)	49	24.4	99	24.1	0.91 (0.61–1.41)
2 or more	16	6.5	53	10.4	0.47 (0.24–0.89)	14	7	37	9.0	0.67 (0.33–1.37)
					Ptrend = 0.001					Ptrend = 0.3
Other allergy[f]										
No	233	92.8	477	91.9	1.00	186	90.3	362	86.2	1.00
Yes	18	7.2	42	8.1	0.74 (0.40–1.36)	20	9.7	58	13.8	0.80 (0.45–1.41)

[a]ORs were adjusted for educational level and mobile phone use

[b]Any allergy was considered positive if asthma or eczema or hay fever was reported as diagnosed by a physician

[c]Asthma status not known for one glioma case and one meningioma case

[d]Eczema status not known for two meningioma cases

[e]Hay fever status not known for five glioma cases and two meningioma cases

[f]Other allergies not known for two glioma cases

found a significant inverse association between hay fever and risk of glioma (OR 0.46, 0.30–0.72). Inverse associations were also observed for asthma (OR 0.70), eczema (OR 0.72) and other types of allergy (OR 0.74) but they were not significant. When we stratified analyses by sex (Table 4), associations were stronger in women: a history of any allergy was associated with a significant 61% decrease in risk of glioma (OR 0.39, 0.23–0.69), the trend of risk with the number of conditions remained significant (p-trend = 0.002) and hay fever was associated with a 59% decrease in risk (OR 0.41, 0.22–0.78). Other allergic conditions were also associated with a decreased glioma risk but associations remained non-significant (OR 0.57 for asthma, OR 0.72 for eczema and OR 0.47 for other types of allergy). In men, we observed a significant inverse association between risk of glioma and hay fever (OR 0.49; 0.26–0.90) and inverse associations with any allergy and more specifically with asthma and eczema were non-significant.

Sensitivity analyses were presented in supplemental tables. When proxy respondents were excluded from analyses and when analyses were adjusted for alcohol consumption, the inverse associations with any allergy and hay fever were somewhat attenuated. However, further adjustment for smoking status, occupational exposure to pesticides, living on a farm during the first year of life or other allergic conditions did not change the results. When reference group was restricted to subjects with no allergic condition at all in individual allergy analyses, the association with rhinitis was strengthened (OR 0.41; 0.23–0.73) and the association with other allergy was inversely associated with glioma (OR 0.33; 0.12–0.93). When the trend test across the number of allergic conditions was repeated for affected subjects only, the test was not significant (ptrend = 0.9).

Table 4 Adjusted ORs (95% CIs) for glioma in relation to a history of any allergy or specific allergic conditions by sex, CERENAT, 2004–2010

	Men				OR (95% CI)[a]	Women				OR (95% CI)[a]
	Cases (n = 143)		Controls (n = 299)			Cases (n = 110)		Controls (n = 225)		
	N	%	N	%		N	%	N	%	
Any allergy[b]										
No	107	76.4	195	66.3	1.00	82	75.2	124	56.6	1.00
Yes	33	23.6	99	33.7	0.62 (0.37–1.05)	27	24.8	95	43.4	(0.39 0.23–0.69)
Asthma										
No	132	93	278	93	1.00	103	93.6	203	90.2	1.00
Yes	10	7	21	7	0.88 (0.35–2.25)	7	6.4	22	9.8	0.57 (0.23–1.43)
Eczema										
No	127	88.8	260	87.2	1.00	224	88.5	440	84.6	1.00
Yes	16	11.2	38	12.8	0.92 (0.46–1.84)	29	11.5	80	15.4	0.72 (0.44–1.16)
Hay fever										
No	121	87.0	221	75.2	1.00	94	86.2	158	72.1	1.00
Yes	18	13.0	73	24.8	0.49 (0.26–0.90)	15	13.8	61	27.9	0.41 (0.22–0.78)
Number of allergies										
0	107	77.5	195	66.5	1.00	82	75.2	124	57.4	1.00
1	22	16.0	70	23.9	0.61 (0.34–1.10)	20	18.4	67	31.0	0.44 (0.24–0.80)
2 or more	9	6.5	28	9.6	0.64 (0.27–1.51)	7	6.4	25	11.6	0.34 (0.12–0.90)
					Ptrend = 0.1					Ptrend = 0.002
Other allergy										
No	129	91.5	277	93.9	1.00	104	94.5	200	89.3	1.00
Yes	12	8.5	18	6.1	1.28 (0.53–3.09)	6	5.5	24	10.7	0.47 (0.19–1.20)

[a]ORs were adjusted for educational level and mobile phone use

[b]Any allergy considered positive if asthma or eczema or hay fever was reported as diagnosed by a physician

Meningiomas

Adjusting for educational level and mobile phone use, no significant association was observed between the risk of meningioma and a history of any allergy or specific allergic conditions. However, a decreased risk of meningioma was suggested with a history of any allergy (OR 0.87, 0.60–1.28), specifically for eczema (OR 0.66, 0.39–1.12). As observed in the supplemental tables, sensitivity analyses restricted data to participants who were self-respondents, additional adjustment for alcohol consumption, smoking status, occupational exposure to pesticides, living on a farm during the first year of life or other allergic conditions produced little change in ORs. When the reference group was restricted to subjects with no allergic condition at all in individual allergy analyses, the results were unchanged. When we stratified analyses by sex (Table 5), no significant association was observed between the risk of meningioma and a history of any allergy or specific allergic conditions in both sexes.

Discussion

The CERENAT case-control study was one of the few studies that examine the association between allergic conditions and the risk of glioma and meningioma, taking into account a large variety of potential lifestyle and environmental risk factors such as smoking status, alcohol consumption, dietary intake, occupational exposure to pesticide, and RFs via mobile phone use. We found that a history of any allergy and specifically hay fever were significantly associated with reduced glioma risk, with a dose–response effect with the number of allergic conditions reported and these associations were strengthened in women. Furthermore, our findings suggest that a history of allergy, and specifically eczema, may be associated with a lower risk of meningioma but these associations were not significant.

In previous analyses of the present study [24, 25], a significant increased risk of CNS tumors, especially gliomas was observed in the heaviest users of mobile phone compared to the non-users and several associations were

Table 5 Adjusted ORs (95% CIs) for meningioma in relation to a history of any allergy or specific allergic conditions by sex, CERENAT, 2004–2010

	Men				OR (95% CI)[a]	Women				OR (95% CI)[a]
	Cases (n = 49)		Controls (n = 100)			Cases (n = 157)		Controls (n = 321)		
	N	%	N	%		N	%	N	%	
Any allergy[b]										
No	37	75.5	67	67.7	1.00	101	65.6	208	66	1.00
Yes	12	24.5	32	32.3	0.72 (0.28–1.84)	53	34.4	107	34	0.92 (0.60–1.41)
Asthma										
No	46	93.9	90	90	1.00	143	91.7	297	93.1	1.00
Yes	3	6.1	10	10	0.76 (0.17–3.40)	13	8.3	22	6.9	1.14 (0.56–2.35)
Eczema										
No	42	87.5	85	85	1.00	136	87.2	265	83.3	1.00
Yes	6	12.5	15	15	0.62 (0.18–2.19)	20	12.8	53	16.7	0.65 (0.36–1.18)
Hay fever										
No	43	87.8	82	83.7	1.00	121	78.1	249	78.5	1.00
Yes	6	12.2	16	16.3	0.64 (0.15–2.75)	34	21.9	68	21.5	0.97 (0.59–1.58)
Number of allergies										
0	37	77.1	67	68.4	1.00	101	66.0	208	66.4	1.00
1	8	16.7	23	23.4	0.83 (0.27–2.54)	41	26.8	76	24.3	0.97 (0.61–1.54)
2 or more	3	6.2	8	8.2	0.48 (0.08–2.89)	11	7.2	29	9.3	0.70 (0.31–1.56)
					Ptrend = 0.4					Ptrend = 0.4
Other allergy										
No	47	95.9	89	89.0	1.00	139	88.5	273	85.3	1.00
Yes	2	4.1	11	11.0	0.79 (0.15–4.16)	18	11.5	47	14.7	0.82 (0.45–1.50)

[a]ORs were adjusted for educational level and mobile phone use

[b]Any allergy considered positive if asthma or eczema or hay fever was reported as diagnosed by a physician

found between CNS tumors and dietary habits including an unexpected inverse association with daily alcohol intakes. However, this result may be due to various biases: cases may underreport alcohol consumption because they fear that their lifestyle has caused the disease or because of memory disorders.

The negative association between a history of allergy and glioma risk is consistent with previous meta-analyses [13–15] and the GICC study [12], all estimating a 20–40% decreased risk of glioma associated with a history of allergy, but the associations we found were stronger than this range. Regarding asthma and eczema, although our results were not significant, they were concordant with these and another meta-analysis [16]. Our data suggest that hay fever may largely drive the association between allergy status and glioma risk (OR 0.52, 0.36–0.75 for allergy; OR 0.46, 0.30–0.72 for hay fever). Previous studies also reported a decreased risk associated with hay fever or allergic rhinitis but their effects were not as pronounced as in our study [14, 27, 28]. For example, the meta-analysis of Chen et al., combining data from five case-control studies, provided an OR of 0.78 (0.70–0.87) for hay fever and glioma risk [14]. The INTERPHONE case-control study including data from five countries found a pooled OR of 0.67 (0.53–0.86) for hay fever [28]. Similarly, a UK case-control study reported an OR of 0.73 (0.59–0.90) associated with hay fever [27].

The present study found a significant trend in the reduction of glioma risk with the number of allergy conditions reported (asthma, eczema and/or hay fever), in accordance with the results of two previous case-control studies [18, 29]. Shoemaker et al. did not observe significant associations with the number of conditions reported in a UK study but analyses were restricted to affected subjects only [27]. It is possible that the number of conditions can be related to the activity of the immune system or severity of allergy and subjects with multiple conditions were more likely to be classified correctly as allergic [27, 29].

We also observed different associations with glioma risk according to gender: the associations with a history of allergy, the number of allergies and hay fever were more pronounced in women than in men. Similarly, in a UK population-based case-control study, associations with allergic conditions were somewhat stronger for women than men, but not consistently or significantly [27]. In addition, two case-control studies reported a more pronounced reduction in the risk of glioma associated with the level of allergen-specific-IgE

in women [30, 31]. The reason is unclear but it might be from the inherent difference in immune systems between men and women; steroid sex hormones may affect the strength of immune responses in opposite directions, with stronger immune responses in women than in men [32]. Furthermore, it appears that female sex hormones enhance type 2 responses related to humoral immunity whereas testosterone suppresses type 2 responses in males. Such a different role of allergy in glioma risk between men and women needs to be confirmed.

Regarding meningioma risk, our data suggested no significant association with a history of doctor-diagnosed allergy or specific allergic condition. However, a trend towards a decreased meningioma risk seemed to emerge with eczema (OR 0.66, 0.39–1.12). Three meta-analyses showed conflicting results. The meta-analysis of Linos et al., including six studies on meningioma, found no association between allergy and meningioma [15]. Another, including seven studies, was in line with this conclusion when considering overall allergy but found a decreased risk for eczema [22]. The most recent meta-analysis, including three more case-control studies, found that allergic conditions, asthma and eczema but not hay fever were associated with a reduced risk of meningioma [23].

The possible role of allergic conditions in the development of brain tumors remains poorly understood. One hypothesis is that allergies may represent a heightened state of immunosurveillance: the presence of a hyperactive immune system may subsequently prohibit abnormal cell growth or proliferation but the specific mechanism by which this state of immunosurveillance could help reduce tumor growth remains unexplained [12, 15, 17]. Another explanation is that IgE antibodies against certain allergens may display some cross-reactivity to brain tumor antigens [30]. Another possible scenario is that of immune prophylaxis, in which allergy symptoms themselves, triggered by IgE, serve to expel foreign toxins or pathogens that might be mutagenic [33]. Regardless of the mechanism, experimental evidence indicates that circulating IgE may impede early tumor development [30]. Additionally, reverse causality is possibly another explanation for the protective role of allergies, with the tumor itself suppressing immune function [31]. However, because inverse associations were also observed when allergies developed at an early age or when they were present many years before the brain cancer diagnosis, reverse causality is unlikely to be responsible for the overall findings [15].

This multicenter study was conducted on the general population, and covered various socioeconomic statuses and environmental and occupational exposures, including potential risk factors for brain tumors such as exposure to pesticides, RFs. Cases were included from a clinical network supported by population-based cancer registries, thereby ensuring the reliability of the diagnoses. Controls were randomly selected from the electoral rolls, which include 90% of persons over 18 years, and are representative of the French adult population regarding age and sex [24]. Participation rates (66 and 75% for glioma and meningioma cases, respectively, and 45% for controls) were similar to those reported in previous studies [28, 29]. Unfortunately, the lack of a questionnaire for non-participants prevented us from accurately assessing selection bias. However, the study was presented to participants as dealing with environmental and occupational factors and health in general, the interest in allergy was not mentioned, and the risk of selection bias was therefore reduced.

Some interviews had to be conducted with a proxy because of the health status of the cases, particularly for glioma cases. The rate of proxy respondents for glioma cases was similar to that observed in other case-control studies (23%) and that of meningioma cases was low (5%) [14, 23]. A simplified questionnaire was used in proxies for cases and in matched controls to prevent any differential bias related to simplified questions, even though the quality of data obtained from proxies remains questionable for cases. However, analyses excluding proxy responses did not change the results. In addition, a previous meta-analysis provided evidence that the associations reported in case-control studies of atopy and glioma risk are unlikely to be due to bias from proxy respondents [14]. We lacked information on biomarkers of atopy such as total serum IgE and specific IgE levels, types of allergens or allergy tests detecting specific IgE but questions on allergic conditions were based on a doctor's diagnosis which should minimize the reporting bias. Another issue is the possibility that glioma cases may not remember past exposures accurately due to cognitive impairments. However, the prevalence of any allergy in glioma cases was similar to that reported in previous studies [27, 34, 35] and the associations we found here have also been reported in prospective cohort studies and meta-analyses [13–15, 36].

In conclusion, the CERENAT case-control study offered a unique opportunity to explore the role of allergic conditions in the occurrence of adult brain tumors adjusting for a wide variety of potential lifestyle and environmental risk factors, which were rarely taken into account in epidemiological studies. Our findings confirm the inverse association between allergic conditions and glioma, particularly for hay fever/allergic rhinitis and with a more pronounced effect in women. However, no association was found with meningioma risk which may question the potential protective effect of allergies on this subtype of brain tumors. Future research is needed to clarify the biological mechanism of overall and specific allergic conditions on the risk of glioma and to confirm their different effects by gender.

Acknowledgements We thank the interviewers of CERENAT study: Christine Auguin, Gaëtane Blaizot, Anne-Sophie Lacauve, Elodie Niez, Xavier Schwall and Sandrine Schwall. We also thank Anne Jaffré and Véronique Loyant for their invaluable contribution to the study. The CERENAT study received funding from the following French public research agencies: French National Institute of Health and Medical Research (INSERM), the French agency for Food, Environmental and Occupational Health Safety (ANSES), French Cancer Research Association (ARC - réseau ARECA) and the French League against Cancer (Ligue contre le Cancer - Comité Aquitaine Charentes).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent "Informed consent was obtained from all individual participants included in the study."

References

1. Pouchieu C, Baldi I, Gruber A et al (2015) Descriptive epidemiology and risk factors of primary central nervous system tumors: current knowledge. Rev Neurol (Paris). https://doi.org/10.1016/j.neurol.2015.10.007
2. Samanic CM, De Roos AJ, Stewart PA et al (2008) Occupational exposure to pesticides and risk of adult brain tumors. Am J Epidemiol 167:976–985. https://doi.org/10.1093/aje/kwm401
3. Lee WJ, Blair A, Hoppin JA et al (2004) Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst 96:1781–1789. https://doi.org/10.1093/jnci/djh324
4. Provost D, Cantagrel A, Lebailly P et al (2007) Brain tumours and exposure to pesticides: a case-control study in southwestern France. Occup Environ Med 64:509–514. https://doi.org/10.1136/oem.2006.028100
5. Bortkiewicz A, Gadzicka E, Szymczak W (2017) Mobile phone use and risk for intracranial tumors and salivary gland tumors—a meta-analysis. Int J Occup Med Environ Health 30:27–43. https://doi.org/10.13075/ijomeh.1896.00802
6. Grell K, Frederiksen K, Schüz J et al (2016) The intracranial distribution of gliomas in relation to exposure from mobile phones: analyses from the INTERPHONE Study. Am J Epidemiol 184:818–828. https://doi.org/10.1093/aje/kww082
7. Dubrow R, Darefsky AS, Park Y et al (2010) Dietary components related to N-nitroso compound formation: a prospective study of adult glioma. Cancer Epidemiol Biomark Prev 19:1709–1722. https://doi.org/10.1158/1055-9965.EPI-10-0225
8. Michaud DS, Holick CN, Batchelor TT et al (2009) Prospective study of meat intake and dietary nitrates, nitrites, and nitrosamines and risk of adult glioma. Am J Clin Nutr 90:570–577. https://doi.org/10.3945/ajcn.2008.27199
9. Niedermaier T, Behrens G, Schmid D et al (2015) Body mass index, physical activity, and risk of adult meningioma and glioma: a meta-analysis. Neurology 85:1342–1350. https://doi.org/10.1212/WNL.0000000000002020
10. Zhang D, Chen J, Wang J et al (2016) Body mass index and risk of brain tumors: a systematic review and dose-response meta-analysis. Eur J Clin Nutr 70:757–765. https://doi.org/10.1038/ejcn.2016.4
11. Dubrow R, Darefsky AS (2011) Demographic variation in incidence of adult glioma by subtype, United States, 1992-2007. BMC Cancer 11:325. https://doi.org/10.1186/1471-2407-11-325
12. Amirian ES, Zhou R, Wrensch MR et al (2016) Approaching a scientific consensus on the association between allergies and glioma risk: a report from the Glioma International Case-Control Study. Cancer Epidemiol Biomark Prev 25:282–290. https://doi.org/10.1158/1055-9965.EPI-15-0847
13. Zhao H, Cai W, Su S et al (2014) Allergic conditions reduce the risk of glioma: a meta-analysis based on 128,936 subjects. Tumour Biol 35:3875–3880. https://doi.org/10.1007/s13277-013-1514-4
14. Chen C, Xu T, Chen J et al (2011) Allergy and risk of glioma: a meta-analysis. Eur J Neurol 18:387–395. https://doi.org/10.1111/j.1468-1331.2010.03187.x
15. Linos E, Raine T, Alonso A, Michaud D (2007) Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst 99:1544–1550. https://doi.org/10.1093/jnci/djm170
16. Wang G, Xu S, Cao C et al (2016) Evidence from a large-scale meta-analysis indicates eczema reduces the incidence of glioma. Oncotarget 7:62598–62606. https://doi.org/10.18632/oncotarget.11545
17. Wiemels JL, Wiencke JK, Patoka J et al (2004) Reduced immunoglobulin E and allergy among adults with glioma compared with controls. Cancer Res 64:8468–8473. https://doi.org/10.1158/0008-5472.CAN-04-1706
18. Wiemels JL, Wilson D, Patil C et al (2009) IgE, allergy, and risk of glioma: update from the San Francisco Bay Area Adult Glioma Study in the temozolomide era. Int J Cancer 125:680–687. https://doi.org/10.1002/ijc.24369
19. Schwartzbaum J, Seweryn M, Holloman C et al (2015) Association between prediagnostic allergy-related serum cytokines and glioma. PLoS ONE 10:e0137503. https://doi.org/10.1371/journal.pone.0137503
20. Dobbins SE, Hosking FJ, Shete S et al (2011) Allergy and glioma risk: test of association by genotype. Int J Cancer 128:1736–1740. https://doi.org/10.1002/ijc.25483
21. Cui Y, Hill AW (2016) Atopy and specific cancer sites: a review of epidemiological studies. Clin Rev Allergy Immunol 51:338–352. https://doi.org/10.1007/s12016-016-8559-2
22. Wang M, Chen C, Qu J et al (2011) Inverse association between eczema and meningioma: a meta-analysis. Cancer Causes Control 22:1355–1363. https://doi.org/10.1007/s10552-011-9808-6
23. Wang P-F, Ji W-J, Zhang X-H et al (2017) Allergy reduces the risk of meningioma: a meta-analysis. Sci Rep 7:40333. https://doi.org/10.1038/srep40333
24. Coureau G, Bouvier G, Lebailly P et al (2014) Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med 71:514–522. https://doi.org/10.1136/oemed-2013-101754
25. Allès B, Pouchieu C, Gruber A et al (2016) Dietary and alcohol intake and central nervous system tumors in adults: results of the CERENAT multicenter case-control study. Neuroepidemiology 47:145–154. https://doi.org/10.1159/000450580
26. Campbell B, Raherison C, Lodge CJ et al (2017) The effects of growing up on a farm on adult lung function and allergic phenotypes: an international population-based study. Thorax 72:236–244. https://doi.org/10.1136/thoraxjnl-2015-208154
27. Schoemaker MJ, Swerdlow AJ, Hepworth SJ et al (2006) History of allergies and risk of glioma in adults. Int J Cancer 119:2165–2172. https://doi.org/10.1002/ijc.22091
28. Turner MC, Krewski D, Armstrong BK et al (2013) Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. Cancer Causes Control 24:949–960. https://doi.org/10.1007/s10552-013-0171-7

29. Wigertz A, Lönn S, Schwartzbaum J et al (2007) Allergic conditions and brain tumor risk. Am J Epidemiol 166:941–950. https://doi.org/10.1093/aje/kwm203
30. Schwartzbaum J, Ding B, Johannesen TB et al (2012) Association between prediagnostic IgE levels and risk of glioma. J Natl Cancer Inst 104:1251. https://doi.org/10.1093/jnci/djs315
31. Schlehofer B, Siegmund B, Linseisen J et al (2011) Primary brain tumours and specific serum immunoglobulin E: a case-control study nested in the European Prospective Investigation into Cancer and Nutrition cohort. Allergy 66:1434–1441. https://doi.org/10.1111/j.1398-9995.2011.02670.x
32. Roved J, Westerdahl H, Hasselquist D (2017) Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. Horm Behav 88:95–105. https://doi.org/10.1016/j.yhbeh.2016.11.017
33. Sherman PW, Holland E, Sherman JS (2008) Allergies: their role in cancer prevention. Q Rev Biol 83:339–362
34. Schlehofer B, Blettner M, Preston-Martin S et al (1999) Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer 82:155–160
35. Berg-Beckhoff G, Schüz J, Blettner M et al (2009) History of allergic disease and epilepsy and risk of glioma and meningioma (INTERPHONE study group, Germany). Eur J Epidemiol 24:433–440. https://doi.org/10.1007/s10654-009-9355-6
36. Schwartzbaum J, Jonsson F, Ahlbom A et al (2003) Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. Int J Cancer 106:423–428. https://doi.org/10.1002/ijc.11230