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Environmental risk factors for sporadic acoustic neuroma (Interphone Study Group, Germany)

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ABSTRACT

The only known risk factor for sporadic acoustic neuroma is high-dose ionising radiation. Environmental exposures, such as radiofrequency electromagnetic fields and noise are under discussion, as well as an association with allergic diseases.

We performed a population-based case-control study in Germany investigating these risk factors in 97 cases with acoustic neuroma, aged 30 to 69 years, and in 194 matched controls.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in multiple logistic regression models.

Increased risks were found for exposure to persistent noise (OR = 2.31; 95% CI 1.15–4.66), and for hay fever (OR = 2.20; 95% CI 1.09–4.45), but not for ionising radiation (OR = 0.91; 95 % CI 0.51–1.61) or regular mobile phone use (OR = 0.67; 95% CI 0.38–1.19).

The study confirms results of recently published studies, although the pathogenetic mechanisms are still unknown.

1. Introduction

Nerve sheath tumours such as acoustic neuroma (AN) and neuroma of the trigeminal nerve are mostly benign tumours with incidence rates that vary for age and gender worldwide from 1 to 20/1,000,000, influenced by diagnostic methods.[1,2] AN constitutes about 5–6% of all intra-cranial tumours. They occur in a sporadic, mostly unilateral form and a hereditary, mostly bilateral form.[3,4] Not much is known about the aetiology of the sporadic form of AN, but environmental risk factors, such as ionising radiation,[5–9] noise exposure,[10–14] and – most recently – radio frequency electromagnetic fields (RF-EMF), e.g. from mobile phone use,[15–21] as well as an association with allergens, have been reported.[22]

This report shows the results from the German part of an international multi-centre case-control study, conducted by

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the Interphone Study Group and coordinated by the International Agency for Research on Cancer, Lyon.

2. Patients and methods

The German part of the Interphone Study followed the international core study protocol.[23]

2.1. Patients

In four study areas around Bielefeld, Heidelberg, Mainz and Mannheim, comprising 6.6 million inhabitants, we ascertained 106 histological confirmed incident patients of AN, and three patients with neuroma of the trigeminal nerve (WHO International Classification of Diseases-Oncology, version 3: topography codes C72.4 and C72.5 and morphology code 9560/0) treated in the neurosurgical clinics of the four cities, or in the Department of Otolaryngology, Head and Neck Surgery of the University of Mainz. Only patients diagnosed between October, 2000 and October, 2003, aged 30 to 59 years, living in the study region at date of diagnosis, and with sufficient knowledge of the German language, were included. The study was extended, from October 1st, 2001, to include patients aged 60 to 69 years. Patients were identified by study staff who visited the hospitals twice a week and by routine checks of the files of the respective neuropathology departments. With the agreement of the responsible physician, most patients were contacted directly in the clinic and were interviewed during their stay in hospital; otherwise they were invited to participate by letter. Of 106 identified patients with AN, seven refused to participate, two died before the interview, and three were lost to follow-up. In one case, a proxy interview was performed because the patient was too ill to answer. Thus, 94 AN and three trigeminus neuroma patients were included in the analyses (participation rate: 89%).

Controls were randomly selected from the compulsory population registries of the respective study regions and were frequency-matched to cases according to gender, age (±2 years) and regional distribution. They were invited by letter to participate and had to have a main residence in the study region at sampling date and sufficient knowledge of the German language. In total, 368 controls were selected, of which 202 (55%) agreed to participate in the interview which normally took place in their home. 139 (38%) refused and 27 (7%) were either too ill to participate, had died, or were lost to follow up.

At the end of the field work, we performed a post-hoc 1:2-matching by assigning two controls to each case, matched on sex, birth year (±2 years), and study region in order to adjust for the time lag in interviewing cases and controls. By means of this method, we censored the exposure period of the controls at the date of diagnosis of the matched case. This was particularly necessary for the analyses of rapidly changing exposures like mobile phone use. The time difference would have led to an overestimation of mobile phone use among controls. Post-hoc matching accounts for this potential bias, because we obtained a distribution of reference dates among the controls identical to the distribution of diagnosis dates among cases. Eight controls were not matched to any case and excluded from the analysis. Thus, 194 controls were included in the analysis.

2.2. Questionnaire/materials

In computer-assisted personal interviews all participants were asked about mobile phone use, including date of first use, number of calls and duration of calls in all time periods of use, and the use of cordless phones or other transmitters. Persons who were regular users (at least one incoming or outgoing call per week for a period of 6 months or more) were defined as 'exposed'. Lifetime number of calls and the lifetime number of hours of mobile phone use were categorised into four groups (never regular user, $\leqslant$50%, >50%–75%, and >75% during all time periods). The cut-offs of these categories are based on the empirical distribution among all controls of the German Interphone Study, including the controls for glioma and meningioma patients (see Table 2). The use of headsets with a microphone and the use of hands-free devices in vehicles were taken into account by reducing the cumulative use accordingly.

Participants were also asked about exposure to RF-EMF, to ionising radiation, and to occupation related to loud noise including e.g. source and duration of exposure. Questions were constructed by the Interphone Exposure Assessment Committee. An exposure matrix for occupational RF-EMF activity was constructed on the basis of an expert rating using information on year of first exposure, numbers of years exposed and distance to the EMF source. 'High' exposure was defined as an exposure that exceeds the general exposure limits of RF-EMF recommended by the International Commission on Non-Ionising Radiation Protection (ICNIRP). (For details see Berg and colleagues 2006).[24] For noise exposure, additionally, character of noise ('persistent', 'intermittent', 'rare but strong, e.g. explosion') and the use of noise protection devices were asked for.

Additional information on ionising radiation for diagnostic (including teeth) and therapeutic purposes, and on magnetic resonance imaging (MRI) examinations of the head and neck, on the occurrence of specific diseases, such as asthma, hay fever, eczema, hearing loss, tinnitus, which had been diagnosed by a physician, and on smoking was also collected. None of the study participants reported a neurofibromatosis or tuberous scleroses. Epilepsy was only reported by one control.

For the analyses, only exposures which occurred at least 2 years before the tumour diagnoses (for cases), or reference date (for controls), were taken into account. Cumulative exposure to mobile phones was the only variable calculated until date of diagnosis or reference date.

2.3. Statistical analyses

For the analyses, cases with AN and those with neuroma of the trigeminal nerve were combined. Multiple conditional logistic regression models for frequency-matched data sets were used to estimate the OR and its respective 95% CI.[25] All analyses were stratified by gender and adjusted for centre (Bielefeld, Heidelberg-Mannheim, and Mainz), age at diagnosis (linearly), socio-economic status (SES; low, intermediate, high), and living in an urban area (more than 100,000 inhabitants versus other). Adjustment for smoking was performed when ORs related to occupations and aller-

gies were estimated. Smoking exposure was categorised into three groups: never, current and ex-smokers (for at least 2 years before date of diagnosis or reference date). The definition of SES is based on the highest school education and occupational or academic grade in Germany. The one proxy interview for a case was included in the basic analyses but excluded when detailed analyses were performed. As there were only a few missing values for the various analyses, the participants were excluded from the respective analyses.

Data on self-reported occupational and recreational exposure to noise were analysed in a model together with the type of noise, taking into account the permanent use of noise protection devices. These were defined as 'not exposed'.

3. Results

97 cases and 194 matched controls were included in the analyses. Demographic characteristics of the study participants are shown in Table 1. There were slightly more men (53%) than women and most patients (54%) were 50 years or older, married or living in a partnership (85%), and residing in rural areas (75%). These distributions were similar in controls. However, compared to the cases, more controls had a higher socio-economic status and more controls were current smokers.

Exposure to RF-EMF was not associated with the risk of AN (Table 2). Regular use of mobile phones resulted in an OR of 0.67 (95% CI 0.38–1.19). The risk was similar for those participants who started using a mobile phone more than 5 years before the reference date. No case reported the use of a mobile phone for more than 10 years. With the increasing number of calls or duration of calls, the risk of developing an AN did not increase. For persons with more than 4350 cumulative calls, the OR was 0.22 (95% CI 0.06–0.80), and for persons who used the mobile phone for more than 195 hours in total, the OR was 0.35 (95% CI 0.12–1.01). Adjusting for hearing loss or other confounder variables did not alter the risk substantially (data not shown).

17 patients and 23 controls reported an occupational exposure to RF-EMF. Compared to those not exposed or not highly exposed to RF-EMF, highly exposed persons showed a non-significantly increased risk (OR = 1.48; 95 % CI 0.53–4.13). However, this analysis was based on very small numbers of exposed persons (seven patients and ten controls). Adjustment for smoking did not alter the risk.

Exposure from MRI (OR = 0.89; 95% CI 0.44–1.82) and from diagnostic and therapeutic (only three cases and one control)

Table 1 – Demographic characteristics of acoustic neuroma cases and population controls, Germany 2000–2003

	Cases (n = 97)		Controls (n = 194)	
	Numbers (n)	%	Numbers (n)	%
Gender				
men	51	53	102	53
women	46	47	92	47
Age groups				
⩽39 years	22	23	41	21
40–49 years	23	24	47	24
50–59 years	25	26	48	25
⩾60 years	27	28	58	30
Socio-economic status[a]				
low	6	6	8	4
medium	64	66	107	54
high	27	28	79	41
Marital status				
single	5	5	14	7
married/partner	82	85	163	84
divorced	5	5	6	3
widowed	5	5	11	6
Living area[b]				
urban	24	25	52	27
rural	73	75	142	73
Smoking[c]				
never	58	60	81	42
ex-smoker	27	28	59	30
current	12	12	54	28
Self interviews	96	99	194	100
Proxy interviews	1	1	–	–

a Based on the highest school education and occupational or academic grade in Germany.
b Urban = ⩾100,000 inhabitants; rural = <100,000 inhabitants.
c Smoking exposure at least 2 years before tumour diagnosis (reference date for controls, respectively).

Table 2 – Distribution of RF-EMF in cases and population controls and the risk of acoustic neuromas (*n* = 97 cases/*n* = 194 controls), Germany 2000–2003

	Cases		Controls		OR[a]	95% CI[b]
	n	%	*n*	%		
Regular mobile phone use						
never use	68	70	120	62	1.00	–
ever use	29	30	74	38	0.67	0.38 – 1.19
Time since first regular use						
never or <1 year use	69	71	121	62	1.00	–
1–4 years	20	21	43	22	0.78	0.40 – 1.50
5–9 years	8	8	27	14	0.53	0.22 – 1.27
10+ years	0	0	3	2	–	–
Life-time number of calls[c]						
never use	67	70	120	62	1.00	–
⩽1176	17	18	32	16	0.88	0.43 – 1.78
>1176–⩽4350	9	9	19	10	0.87	0.36 – 2.09
>4350	3	3	23	12	0.22	0.06 – 0.80
Life-time duration of calls (hours)[c,d]						
never use	67	71	120	62	1.00	–
⩽44	16	17	27	14	1.04	0.51 – 2.16
>44–⩽195	7	7	21	11	0.58	0.22 – 1.48
>195	5	5	25	13	0.35	0.12 – 1.01
Specified occupational exposure[e]						
not or not highly exposed	90	93	184	95	1.00	–
highly exposed	7	7	10	5	1.45	0.51 – 4.19

a Odds ratio (OR) from conditional logistic regression for frequency-matched data sets; adjusted for SES, living area urban/rural, age at diagnosis and study centre.
b 95% confidence interval (CI).
c One case = proxy interview is excluded.
d For one case and one control, data are missing.
e Additionally adjusted for smoking.

Table 3 – Risk of acoustic neuroma by self-reported noise exposure[a] from cases and population controls (*n* = 94 cases/*n* = 190 controls[b]), Germany 2000–2003

	Cases		Controls		OR[c]	95% CI[d]
	n	%	*n*	%		
Self-reported noise exposure						
Not exposed[e]	48	51	122	64	1.00	–
Ever exposed in leisure time only	6	6	17	9	0.96	0.35 – 2.63
Ever exposed in occupation:						
Noise character: persistent	22	23	23	12	2.31	1.15 – 4.66
intermittent	9	10	22	12	1.01	0.42 – 2.43
explosive	2	2	2	1	2.49	0.32 – 19.32
Exposed but situation missing	7	8	4	2	6.72	1.75 – 25.82

a Exposed at least 2 years before tumour diagnosis (reference date for cases, respectively).
b For three cases and four controls, data for noise exposure are missing; therefore, participants are excluded from further analyses.
c Odds ratio (OR) from multiple conditional logistic regression for frequency-matched data sets; adjusted for SES, living area urban/rural, age at diagnosis and study centre.
d 95% confidence interval (CI).
e Participants always using noise protection devices are regarded as 'not exposed' (*n* = 7).

ionising radiation (OR = 0.91; 95% CI 0.51–1.61) showed no association to the risk of AN. For persons with first exposure prior to 25 years of age, the OR was 1.05; (95% CI 0.49–2.23) and for those older than 25 years, it was 0.84 (95% CI 0.45–1.57) (adjusted for occupational exposure to ionising radiation).

ORs for noise exposure are presented in Table 3. Seven cases and four controls reported an exposure to noise without additional information. Self-reported occupational exposure showed an increased OR of 2.31 (95% CI 1.15–4.66) for those who reported exposure to persistent noise compared to those

Table 4 – Distribution of asthma, hay fever and eczema in cases and population controls and the risk of acoustic neuromas (*n* = 97 cases/*n* = 194 controls), Germany 2000–2003

	Cases Yes		Controls Yes		OR[a]	95% CI[b]
	n	%	*n*	%		
No allergies at all	61	63	143	74	1.0	–
Asthma[c]	9	9	13	7	1.06	0.40 – 2.82
Hay fever[c,d]	22	23	21	11	2.20	1.09 – 4.45
Eczema[c]	16	17	25	13	1.11	0.51 – 2.38

a Odds ratio (OR) from multiple conditional logistic regression for frequency-matched data sets; adjusted for SES, living area urban/rural, age at diagnosis, study centre and smoking.
b 95% confidence interval (CI).
c Diagnosed at least 2 years before tumour diagnosis; multiple assessments are possible.
d For one control age at first diagnosis of hay fever is unknown, therefore, this control was excluded from the analysis.

who did not report exposure to noise. The OR for the exposure to rare but extremely loud noise, like explosions, is based on two cases and two controls only. Recreational exposure to noise was not associated with an increased risk.

The OR for ever/never self-reported occupational exposure without taking the type of the noise into consideration yields an OR = 1.73 (95% CI 0.96–3.12). Additional adjustment for hearing loss and tinnitus revealed a lower OR of 1.15 (95% CI 0.55–2.42).

Hearing problems have been reported by more than 34% of the cases compared to 13% of the controls. Similarly, 23% of the cases but only 7% of the controls suffered from tinnitus with an onset of more than 2 years before the reference date. Thus, hearing loss and tinnitus were highly associated with AN, even when occurring more than 2 years before tumour diagnosis (OR = 3.84; 95% CI 2.01–7.32 and OR = 3.87; 95% CI 1.83–8.20 respectively). Counting events that occurred 5 years before the tumour diagnosis, the ORs for hearing loss and for tinnitus were still increased (OR = 2.43; 95% CI 1.21–4.90 and OR = 2.18; 95% CI 0.89–5.38, respectively).

70% of the cases with unilateral hearing loss reported this for the same side where the tumour occurred, in 24% both ears were affected and about 6% reported hearing loss on the contra-lateral side. Similarly, 79% reported unilateral tinnitus on the same side where the tumour later occurred; 13% had symptoms on both sides and 8% on the contra-lateral side. In contrast, about half of the controls who were suffering from hearing loss and tinnitus reported to have symptoms in both ears (50% hearing loss and 57% tinnitus).

The ORs for allergic diseases are presented in Table 4. For study participants with hay fever the OR was 2.20 (95% CI 1.09–4.45), whereas no increased ORs were found for asthma and eczema.

4. Discussion

This is the first population-based case-control study in Germany investigating environmental risk factors for AN.

Incidence studies describe a slightly higher percentage of women suffering from this disease.[3] In our study we ascertained a slightly higher number of men than of women, as did an US study[1] and a recent Swedish study.[10] This might have been due to random variation, or due to selection bias as we cannot exclude that patients with small AN were treated in clinics other than the ones we used for case ascertainment. However, routine checks of pathology departments covering the study areas did not show many missing patients and those identified by this search were included. Diagnostic procedures can be considered as constant for all our 97 cases. The time difference between diagnostic imaging (MRI) and histological confirmation was on average less than 3 months.

A strength of our study is the population based ascertainment of controls. However, this approach generated a lower participation rate of controls than cases which is a possible limitation of our study, as it might have introduced selection bias. We do not believe this bias to be substantial, because the distribution of controls in the demographic data, especially for smoking and SES are in line with what we expected from other studies.[26] Controls were usually interviewed later than their matched case, but as the average time lag was 170 days, we don't think this added a material extra burden for controls to recall past events.

We did not identify an increased risk from RF-EMF exposure, including the use of mobile phones and occupational exposure. Although we cannot exclude an influence due to selection bias, our results are in line with those from several recent publications.[15,16,18–21] A small increased risk of AN has previously been described regarding the use of mobile phones for more than 10 years, but this concerns mostly the use of analogue mobile phones.[17,19] However, due to small numbers, neither long-term exposure nor exposure from analogue mobile phones could be investigated in our study. The latter were not very common in the German population.

Details of other sources of exposure to RF-EMF from specific occupational activities, such as using different kinds of transmitters and ham radios, or working with or nearby broadcasting and telecommunication antennas were carefully documented during the interview. However, only a few people were identified as highly exposed to RF-EMF; therefore, the observed OR has to be interpreted with caution.

Ionising radiation is mentioned as a risk factor for AN. Results from cohort studies reported an elevated risk, while results from case-control studies are not consistent.[6,7,9,12] We have not found an association between AN and ionising radiation, either exposed for diagnostic or therapeutic reasons (but note the small numbers) or from occupational exposures. We cannot exclude that our results are biased by differential recall effects.

An association between exposure to occupational noise and AN was first published in 1989.[12] In our study a twofold increased risk was observed for those persons who reported to have been exposed to persistent noise, but not for those exposed to intermittent noise. In all analyses, noise protection devices and hearing problems have been taken into account. With regard to recreational exposure to noise, the number of exposed persons was too small to obtain meaningful results. Nevertheless, differential misclassification of noise exposure may be a problem. Our results are a further confirmation of published or anecdotal knowledge that noise might be associated with an increased risk of developing AN. However, we cannot determine whether noise is a risk factor for AN or whether AN, a slowly growing benign tumour, is diagnosed more frequently in persons who are examined because of hearing loss and tinnitus, possibly as a consequence of permanent loud noise exposure. In the early 1980s, observations were published showing that AN was found more frequently than expected in workers exposed to noise and tested by audiometric tests in the frame of occupational safety regulations.[13,14] These observations were confirmed by others[11,27,28] who concluded that patients with noise-induced asymmetrical hearing loss should be screened for AN. In 1990 a case report discussed trauma[29] as a possible cause of AN. Experimental studies in rodents have shown that severe acoustic trauma (such as impulse noise) causes mechanical damage of the VIIIth nerve and the surrounding tissue.[30] It has been hypothesised that nerve growth factors acting locally and for a limited time might also induce the tumour after injuries.[29,30] A study published in 1989 mentioned that 'the mechanisms by which trauma may relate to tumour development involve the cell proliferation which occurs during repair process' and hypothesised that this may promote cell proliferation if an AN was primarily initiated by exposure to a carcinogen.[10,12]

The role of atopic diseases for the development of brain tumours in adults was investigated in several epidemiological studies and showed that hay fever, allergy to food and allergy to other substances were associated with significantly increased risks of AN.[22] Our study confirms the association between AN and hay fever, but not with other allergic diseases. Chronic infection of the auditory tubes due to hay fever might be responsible for this effect. The influence of chronic immune cell activation of Th1 or Th2 (helper T-cells type 1 and type 2) mediated autoimmune diseases is discussed for malignancies. Whether these mechanisms are also of relevance to the development of benign tumours, like AN, has not yet been addressed. However, this cannot be examined by an epidemiological study like ours. Recall bias and detection bias also have to be taken into account.[22] In 2004, a study investigating the association between hay fever and polymorphisms in Th1, Th2 and cytokine genes found that hay fever reported by the study participants and the respective polymorphisms in genes are highly associated.[31] This argues against a differential misclassification between patients and control persons.

The frequent occurrence of hearing loss and tinnitus might be interpreted as early symptoms of AN as it is also described in several previous publications.[27,28,32]

In conclusion, we found that exposure to persistent noise in occupational activities increased the risk for AN and there was also an association with hay fever. However, exposure to ionising radiation or to radio-frequency electromagnetic fields, e.g. from mobile phones, did not increase the risk.

Conflict of interest statement

None declared.

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