SHORT REPORT

Influence of age on the association between primary hemifacial spasm and arterial hypertension

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Objective: To investigate the association between primary hemifacial spasm and arterial hypertension.

Subjects: 114 patients with primary hemifacial spasm and 228 neurological controls, matched for age, sex, and referral centre, were recruited during an 18 month period from consecutive outpatients attending two neurological institutions.

Design: The association between exposure variables and case/control status was examined in conditional logistic regression models, adjusting simultaneously for disease duration and education level.

Results: Hypertension was more common among the patients with primary hemifacial spasm than among the controls. The association was independent of age, disease duration, years of schooling, and other diseases (adjusted odds ratio (OR) 2.76 (95% confidence interval (CI), 1.43 to 5.33); $p = 0.002$). Hypertension was associated with hemifacial spasm in both the left sided group (adjusted OR, 2.76 (1.18 to 6.44); $p = 0.02$) and the right sided group (adjusted OR, 3.02 (1.13 to 8.1); $p = 0.03$). The association of hypertension with hemifacial spasm was apparently greater in the age group < 60 years (adjusted OR, 4.2 (1.4 to 12); $p = 0.008$) than in the age group ≥ 60 years (adjusted OR, 2.5 (CI 1.3 to 4.6); $p = 0.005$), but the difference in the OR estimates between the two age groups was not significant. Among hypertensive patients, mean age at the diagnosis of hypertension was significantly lower than mean age at the onset of hemifacial spasm in the age group ≥ 60 years, but not significantly different in the age group < 60 years.

Conclusions: The findings support the hypothesised association of primary hemifacial spasm with hypertension and raise the possibility that a different mechanism underlies the association in different age groups.

Two recent case-control studies^{1,2} suggested that primary hemifacial spasm may be associated with arterial hypertension, but the relation between the two conditions was not clarified. Primary hemifacial spasm is increasingly attributed to neurovascular compression of the facial nerve,³ and there is evidence suggesting that compression of the ventrolateral medulla (VLM) at the root entry zone of cranial nerves IX and X may induce hypertension.^{4–8} Earlier surgical observations indicated a selective relation between left sided neurovascular compression of the VLM and hypertension.⁴ Because the rostral VLM is close to the origin of the facial nerve, vessel loops originating from the vertebral/basilar arteries or their branches might be responsible for multiple neurovascular compressions, inducing both hemifacial spasm and hypertension.⁹ Alternatively, hypertension could be a risk factor for hemifacial spasm because it may produce vascular anomalies resulting in compression of the seventh cranial

nerve.¹ Under this hypothesis one would expect that hypertension would precede hemifacial spasm, that it would occur equally with left or right sided hemifacial spasm, and that the association between the two conditions would be stronger in older subjects (because of the higher frequency of hypertension in this age group).

We investigated these issues in 114 patients with primary hemifacial spasm and 228 neurological controls recruited during an 18 month period from among consecutive outpatients attending two neurological institutions in the Puglia region, south Italy.

METHODS

During the study period, primary hemifacial spasm was diagnosed in 114 subjects (65 left sided, 49 right sided) according to published criteria.³ Secondary causes were excluded by computed tomography or magnetic resonance imaging (MRI) of the head. Neurovascular compression of the seventh cranial nerve was suspected in 38 of 67 patients who had MRI (56.7%). This was lower than the percentage generally reported,¹⁰ presumably because the study was not designed to include advanced MRI, and because equipment and radiologists differed.

For each case, two control subjects, matched for age (± 5 years), sex, and referral centre, were identified from among outpatients suffering from cephalalgia, epilepsy, head trauma, amyotrophic lateral sclerosis, adult onset dystonia, cerebellar ataxia, and peripheral nerve entrapment syndromes. The participation rate was 100% among cases and 94% among controls. Using two controls per case assured adequate power to test the association of hypertension and hemifacial spasm in the left sided and right sided subgroups. According with the equation reported by Schlesselman¹¹ the study had a greater than 80% chance of detecting a threefold modification in the risk of developing either left sided or right sided hemifacial spasm for the variable hypertension.

As previously reported,² all cases and controls had appropriate clinical, blood, and urine laboratory investigations designed to evaluate hypertension or other diseases potentially associated with hypertension. In particular, systolic and phase V diastolic blood pressures were measured in both arms of all cases and controls (including those receiving antihypertensive drug treatment) using an appropriate sized cuff, with the subject seated and after a 20 minute rest. On each visit, three readings obtained at two minute intervals were averaged. Hypertension was defined as an average systolic blood pressure of ≥ 140 mm Hg and a diastolic pressure of ≥ 90 mm Hg on three separate visits over two to three weeks.¹² At interview, hypertension was diagnosed in four new cases of hemifacial spasm and two controls. Age, sex, years of schooling, age at the onset of hemifacial spasm or control disease, and age at the diagnosis of hypertension were recorded.

The association between exposure variables and case/control status was examined in conditional logistic regression

Table 1 Characteristics of case and control populations

Characteristics	Cases (n=114)	Controls (n=228)	OR (95% CI), p value
Sex (men/women)	40/74	80/148	1
Age (years)			1.06 (0.97 to 1.15), 0.2
Mean (SD)	61.9 (12.3)	61.5 (12.5)	
Median	65	64	
Range	20 to 83	18 to 84	
Duration of disease (years)			1.1 (1.04 to 1.14), <0.001
Mean (SD)	8.2 (6.2)	4.8 (6.69)	
Median	7	1	
Range	1 to 33	1 to 43	
Years of schooling			0.87 (0.83 to 1.1), 0.1
Mean (SD)	5.1 (2.6)	6.3 (4.1)	
Median	5	5	
Range	2 to 13	0 to 18	
Hypertension (n, %)	62, 54%	86, 38%	2.83 (1.6 to 4.9), <0.001
Other diseases (n, %)	15, 13%	11, 5%	3.05 (1.32 to 3.06), <0.01

CI, confidence interval; OR, odds ratio.

Table 2 Age (years) at the diagnosis of arterial hypertension and age at the onset of hemifacial spasm in 62 hypertensive patients

Hypertensive patients	Age at the diagnosis of hypertension	Age at the onset of hemifacial spasm	p Value
All (n=62)	55.8 (10.2)	59.1 (11.0)	0.03
≥60 years (n=49)	58.4 (9.4)	63 (7.5)	0.01
<60 years (n=13)	46.2 (6.0)	44.7 (9.8)	0.6

Values are mean (SD); p values obtained from two tailed paired Student *t* test.

models, always adjusting simultaneously for disease duration and education level. Given the imperfect match on age, estimates were also adjusted for this variable. Odds ratios (OR), 95% confidence intervals (CI), and probability (p) values (likelihood ratio statistics) were calculated using a standard statistical package (Stata 7).

RESULTS

Demographic and clinical features of case and control groups are given in table 1. Cases had a longer duration of disease and a lower level of education than controls. Both arterial hypertension and other diseases (including diabetes, renal failure, and hyperthyroidism) were more common in cases than controls. Stratifying cases by duration of hemifacial spasm showed no increase in the relative frequency of the exposure variables as duration lengthened (not shown). The rate of exposures was similar across control diagnostic subgroups (not shown).

On conditional logistic multivariate regression analysis (done on 114 matched sets), the association of hypertension and hemifacial spasm was independent of age, duration of disease, years of schooling, and other diseases, with an adjusted OR of 2.84 (95% CI, 1.5 to 5.3); $p = 0.001$. In contrast, the association between other diseases and hemifacial spasm was no longer significant after adjusting simultaneously for age, duration of disease, education level, and hypertension (adjusted OR, 2.3 (0.89 to 6.0); $p = 0.084$). Hypertension was significantly associated with hemifacial spasm in both the left sided group (adjusted OR, 2.76 (1.18 to 6.44); $p = 0.02$) and the right sided group (adjusted OR, 3.02 (1.13 to 8.1); $p = 0.03$).

Hypertension was found in two of 14 cases (14%) and three of 38 controls (7.8%) aged < 50 years, in 11 of 26 cases (42%) and nine of 47 controls (19%) aged between 50 and 59 years, and in 49 of 74 cases (66%) and 74 of 143 controls (52%) aged

≥ 60 years. Stratifying by age and taking non-hypertensive patients as a reference yielded a significant association of hypertension with hemifacial spasm both in the age group < 60 years (adjusted OR, 4.2 (1.4 to 12); $p = 0.008$) and in the age group ≥ 60 years (adjusted OR, 2.5 (1.3 to 4.6); $p = 0.005$). In the 37 case patients aged < 60 years, hemifacial spasm was left sided in nine hypertensive patients and 13 non-hypertensive patients, and right sided in four hypertensive patients and 11 non-hypertensive case patients ($\chi^2 = 0.3$, $p = 0.6$). In the 68 case patients aged ≥ 60 years, hemifacial spasm was left sided in 26 hypertensive and 12 non-hypertensive patients, right sided in 22 hypertensive and 8 non-hypertensive case patients ($\chi^2 = 0.03$, $p = 0.8$).

Among hypertensive case patients ($n = 62$), mean age at the diagnosis of hypertension was significantly lower than mean age at the onset of hemifacial spasm in the age group ≥ 60 years, whereas no difference was found in the age group < 60 years (table 2). Mean age at the onset of hemifacial spasm was significantly greater in the age group ≥ 60 years than in the age group < 60 years ($p < 0.0001$). The two groups did not differ for duration of hemifacial spasm (mean (SD): 7.6 (5.1) v 7.1 (8.3) years, $p = 0.86$) or years of schooling (3.8 (1.1) v 4 (1.7), $p = 0.54$).

DISCUSSION

In this series, primary hemifacial spasm was significantly associated with arterial hypertension independently of potentially confounding factors. Though the study design was similar to two previous case-control studies,^{1,2} independent replication of results in different datasets is important in association studies. In addition, our analysis provided new information indicating that left sided and right sided hemifacial spasm both contribute to the association of hemifacial spasm and hypertension, and that age may influence this association.

As this was not a population based study, we corrected for potential bias in case selection by recruiting consecutive patients attending two neurological centres of the same geographical area who met the eligibility criteria during the study period. In this case series the demographic features resembled those in the general population of cases,³ and survival bias was unlikely. To minimise bias caused by overrepresentation of control subjects with diseases associated with exposures, the control series comprised a variety of diagnostic groups with similar rates of exposures. The frequency of hypertension among controls and the increase with age reflected the Italian population in this age group.¹³

The similar contribution of left sided and right sided hemifacial spasm to the association with hypertension is at variance with a previous study by our group.² In that study, arterial hypertension related more strongly to left sided hemifacial spasm. However, data for the right sided group yielded inconclusive results because they lacked statistical power.

As indicated by the odds ratios, the association of hypertension with hemifacial spasm was apparently greater in the age group less than 60 years than in the older subjects. Owing to the small size of the samples, confidence intervals were wide and overlapped, thus indicating that the difference in the odds ratio estimates between the two age groups was not statistically significant. Nevertheless, estimation of confidence intervals suggests that the magnitude of the association between hypertension and hemifacial spasm may be greater in the < 60 years age group than in older subjects. This could be an artefact of selective mortality or the result of confounding by other factors. At present, there are no data to support the selective mortality of patients with hypertensive hemifacial spasm compared with hypertensive controls. Multivariate analysis also excluded confounding by certain demographic and clinical variables.

Hypertension preceded hemifacial spasm in the age group ≥ 60 years, whereas no significant difference was observed in younger patients. This might merely reflect information bias. Retrospective determination of age at the onset of hemifacial spasm by interview can be influenced by several factors, including the time span between the interview and the event, recall motivation, culture, and education. The fact that hypertensive cases aged ≥ 60 years and < 60 years had a similar duration of hemifacial spasm and a similar level of education makes information bias unlikely.

Overall, our findings raise the possibility that different mechanisms underlie the association of hemifacial spasm and hypertension in different age groups. In older patients, hypertension may be a risk factor, possibly by producing vascular anomalies compressing the facial nerve.¹ The other proposed mechanism—multiple neurovascular compressions of the facial nerve and ventrolateral medulla, inducing both hemifacial spasm and hypertension⁹—could be responsible for the presence of both these features in younger patients. In support of this view, neurovascular anomalies may have a genetic basis and may precede the development of hypertension.¹⁴ At variance with earlier uncontrolled surgical observations indicating a selective relation between left sided neurovascular compression of the VLM and hypertension,⁴ recent anatomical

data⁸ and evidence from laboratory animals¹⁵ indicate that the pressor role of the VLM is not associated with laterality. This is consistent with the equal contribution of left sided and right side hemifacial spasm to hypertension in our series. Studies integrating MRI, heart rate variability, and systolic arterial spectral analysis may be necessary to confirm or reject the neurovascular hypothesis of arterial hypertension in hemifacial spasm. Our findings may be of value in designing such studies.

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