Epidemiological Study of Ruptured Intracranial Aneurysms in the Saguenay-Lac-Saint-Jean region (Quebec, Canada)

Jean Mathieu, Louis Pérusse, Pierre Allard, Claude Prévost, Léo Cantin, Jean-Marie Bouchard and Marc DeBraekeleer

ABSTRACT: ***Background:*** Using a population-based register of the Saguenay-Lac-Saint-Jean region (Quebec, Canada), the genealogical reconstruction of 533 individuals with intracranial aneurysm (IA) showed a familial aggregation (the presence of aneurysm in two or more first- to third-degree relatives) for 159 (29.8%) of them; this proportion is much higher than reported elsewhere. ***Objective:*** As part of an ongoing project to assess a genetic predisposition to intracranial aneurysms in the Saguenay-Lac-Saint-Jean population, the objective of the present study was to determine whether age-specific rates of ruptured cerebral aneurysms were higher than in other populations. ***Design:*** A retrospective study of cases of proven ruptured IAs which were hospitalized during the 1973 to 1992 period was conducted. Age-adjusted rates were computed and compared to those reported in the Helsinki population. ***Results:*** We identified 412 cases of ruptured aneurysms. The age-adjusted incidence rate was 7.2/100,000/year (6.2 for men, 8.1 for women), which is similar to the incidence rates reported in other studies. Although the mean age at time of rupture was younger (46.6 years ± 13.8) than usually reported, no increase in age-specific incidence rates was detected. ***Conclusions:*** The results of this epidemiological study neither support nor reject the hypothesis of a genetic predisposition to intracranial aneurysms in the Saguenay-Lac-Saint-Jean population.

RÉSUMÉ: Étude épidémiologique sur les anévrismes intracrâniens rupturés dans la région du Saguenay-Lac-Saint-Jean (Québec, Canada). ***Introduction:*** La reconstruction généalogique de 533 individus atteints d'anévrisme intracrânien (AI), au moyen d'un registre de population de la région du Saguenay-Lac-Saint-Jean (Québec, Canada), a montré une agrégation familiale (la présence d'un anévrisme chez deux cas ou plus qui sont apparentés au premier, deuxième ou troisième degré) chez 159 d'entre eux (29.8%). Cette proportion est bien plus élevée que celle déjà rapportée. ***Objectif:*** Cette étude fait partie d'un projet dont le but est d'évaluer la prédisposition génétique aux AIs dans la population du Saguenay-Lac-Saint-Jean (SLSJ). L'objectif était de déterminer si les taux d'anévrismes cérébraux rupturés ajustés pour l'âge étaient plus élevés que dans les autres populations. ***Conception:*** Il s'agit d'une étude rétrospective de cas prouvés d'AIs rupturés qui ont été hospitalisés entre 1973 et 1992. Les taux ajustés pour l'âge ont été calculés et comparés à ceux rapportés pour la population d'Helsinki. ***Résultats:*** Nous avons identifié 412 cas d'anévrismes rupturés. Le taux d'incidence était de 7.2/100,000/année (6.2 pour les hommes, 8.1 pour les femmes), ce qui est semblable aux taux d'incidence rapportés dans d'autres études. Bien que l'âge moyen au moment de la rupture était plus jeune (46.6 13.8 ans) que ce qui est habituellement rapporté, nous n'avons pas noté d'augmentation dans les taux d'incidence selon l'âge. ***Conclusions:*** Les résultats de cette étude épidémiologique ne supportent ni ne rejettent l'hypothèse d'une prédisposition génétique aux anévrismes intracrâniens dans la population du SLSJ.

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In most populations, subarachnoid hemorrhage (SAH) represents about 10% of all strokes and is an important cause of morbidity and mortality. According to earlier studies, the incidence of SAH secondary to ruptured intracranial aneurysms (IA) varies widely from 1.4 to 27.3/100,000/year.[1] Rate estimations are influenced by type of study, age structure, methods employed for collection of data and criteria adopted to define SAH.[2] For many years, there has been much debate over the etiology of IA as to whether they are congenital or acquired. IA are known to be part of the clinical picture of several hereditary disorders as Ehlers-Danlos type IV syndrome and adult polykystic kidney disease. Whether a genetic predisposition is involved in the genesis of IA without being associated with one of these disorders remains to be proven.

Using the population-based register of the Saguenay-Lac-

Unité de recherche clinique, Hôpital de Chicoutimi, Chicoutimi, (J.M., C.P., L.C., M.D.); Groupe de recherche en épidémiologie de l'Université Laval, Québec, (P.A.); IREP, Université du Québec à Chicoutimi, Chicoutimi, (J.M., L.P.); Hôpital Enfant-Jésus, Québec (J- M.B.).

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Reprint request to: Dr Jean Mathieu, Unité de recherche clinique, Hôpital de Chicoutimi, 305 Saint-Vallier, Chicoutimi, QC, Canada G7H 5H6.

Saint-Jean (SLSJ) population developed and maintained at IREP, the genealogical reconstruction of 533 individuals with IA revealed a familial aggregation for 159 of them (29.8%);[3] this proportion of familial IA is much higher than reported elsewhere. The hypothesis of a new genetic disorder was put forward since several dominant and recessive autosomal disorders have a high prevalence in the SLSJ population.[4,5] A founder effect in the establishment of the French-Canadian population was suggested in this area.[6]

As part of an ongoing project to assess a genetic predisposition to IA in the SLSJ population, the objective of the present study was to determine whether age-specific incidence rates of ruptured IAs were higher than reported elsewhere.

Methods

Sources of medical care and characteristics of the SLSJ population

Medical services in the SLSJ region were provided by five (5) local hospitals (Dolbeau, Roberval, Alma, Jonquière, La Baie) and one regional hospital located in Chicoutimi. Since 1965, neurological services were provided at the Chicoutimi hospital by a team of neurologists and neurosurgeons. In the absence of a neurosurgeon at the Chicoutimi hospital during a 6-year period, neurosurgical services were provided by the Enfant-Jesus Hospital located in Quebec City. Most patients suffering from cerebral hemorrhage, subarachnoid hemorrhage or bloody lumbar puncture were transferred from local hospitals to the Chicoutimi hospital for further investigation and treatment. Occasionally, some patients were directly transferred to the Enfant-Jesus Hospital in Quebec City.

The SLSJ region is a geographically isolated area located in the Northeastern part of the Province of Quebec (Figure 1). The region was opened to white settlement in 1838 and most of its population originated from nearby Charlevoix County. The population grew quickly, first by immigration then naturally. From a few thousands in its early decades, the population rose to 50,000 in 1911 to attain 285,955 in 1991; 98% of the individuals living in SLSJ region are French Canadians. This population shows a young age distribution with 36.1% being ≤19 years

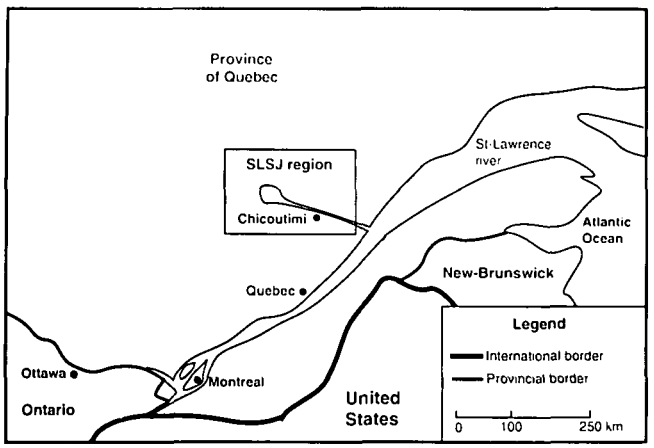

Figure 1: Location of Saguenay-Lac-Saint-Jean (SLSJ) region within the province of Quebec, Canada.

and 18.0% being 50 years or older while these figures for the population of the Province of Quebec are, respectively, 22.1% and 27.9% (Statistics Canada, 1981).

Case ascertainment

Cases were ascertained from a review of medical records in every hospital in the SLSJ region and in the Enfant-Jesus Hospital in Quebec City. We selected all the medical records in which the diagnoses of spontaneous subarachnoid haemorrhage, ruptured intracranial aneurysm and unruptured intracranial aneurysm were recorded during the period 1965-1993. A total of 533 patients with IA were identified (502 ruptured IA, 31 unruptured IA). Patients included in the present epidemiological study are those for which the diagnosis of ruptured IA had been made during the 20-year interval 1973-1992 and were living in the SLSJ region at the time of aneurysm rupture. The diagnosis of ruptured IA had been made either by angiography (11.7%), surgery (2.4%), post-mortem examination (13.8%) or a combination of these procedures (72.1%). Data on location and size of IA were also abstracted from medical records. Posterior communicating artery aneurysms were classified as internal carotid artery aneurysms. Cases of unruptured IA were excluded from this study because the identification of such patients had never been looked for systematically among this population or among other family members. Most of the unruptured IA were confirmed fortuitously during procedures (angiography or surgery) for other reasons than a cerebral hemorrhage; therefore, this incomplete ascertainment of unruptured IA cannot be used for incidence rates calculations. The exclusion of unruptured IA from this study did not change the proportion of familial cases appreciably; the 112 familial cases among 412 ruptured IA represent 27.2% instead of 29.8% in the overall IA population. Cases of SAH secondary to ruptured mycotic aneurysms, rupture of an arteriovenous malformation and trauma were also excluded from the present study.

Statistical analysis

Population numbers over the 20-year interval 1973-1992 were abstracted from the 1971, 1976, 1981, 1986 and 1991 Statistics Canada censuses. For each sex, yearly incident cases by 10-year age-groups were used to calculate crude and age-specific incidence rates per 100,000 person-years. Age-adjusted rates were obtained by applying age-specific rates to the world population. The 95% confidence intervals (CI) for incidence rates were calculated using the normal approximation. The rates were compared to those reported in the Helsinki population using age-adjusted incidence rate ratio (IRR).[7] Confidence limits for the pooled estimate of the IRR were obtained by an approximate method using a directly weighted point estimate. In addition, the 20-year interval was divided into four 5-year periods to evaluate time trends in rates.

Results

Demographic characteristics

During the 20-year interval 1973-1992, 412 cases of ruptured aneurysms were diagnosed in SLSJ region. Female represented 56.8% (234) of these patients. The mean age at aneurysm rupture was 46.6 years (standard deviation (SD)=13.8), ranging from 10 to 81 years old. The mean age for males was 45.3 years (SD

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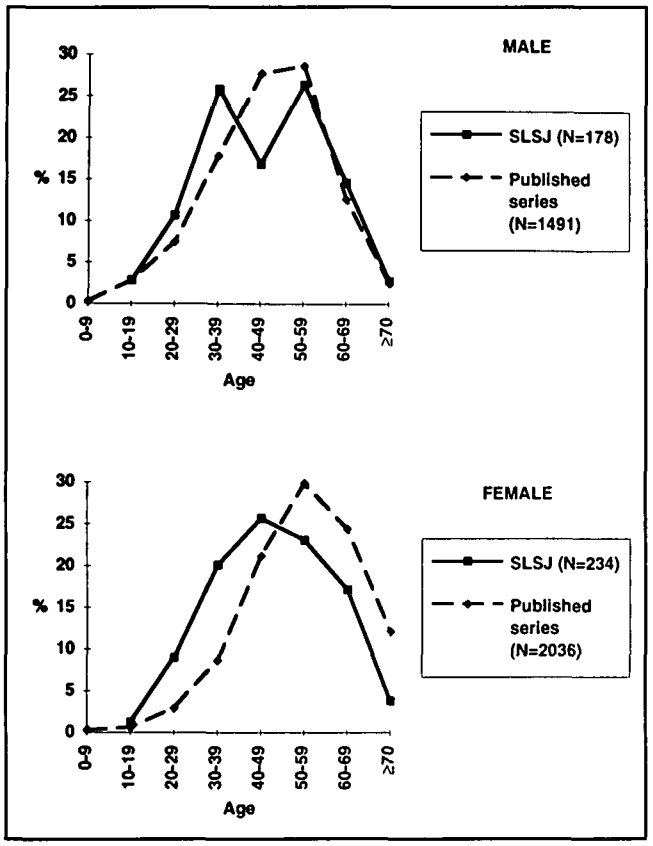

Figure 2: Age distribution of SLSJ patients (N=412) compared with 3527 patients in 6 published series.

=13.9) and for females 47.6 years (SD=13.6). Relative to published series reviewed by Pakarinen,[8] the age distribution was similar for males but slightly younger for females (Figure 2).

Age- and sex-specific incidence rates of ruptured aneurysms

The average annual crude incidence rate was 7.3/100,000 population (95%CI:6.6-8.1), 6.3 for men and 8.4 for women (Table 1). The age-adjusted incidence rate was 7.2/100,000/year (6.2 for men, 8.1 for women) when adjusted to the world population. The incidence rates observed in the SLSJ patients rose inconsistently with age among men, contrary to those among women.

Table 1 also shows that the 1954-61 age-specific incidence rates in Helsinki were similar to those in SLSJ for the whole population (age adjusted IRR 0.87; 95% CI 0.75-1.00) and for females (IRR 0.98; 95% CI 0.81-1.18). For males, the age-adjusted IRR was 0.75 (95% CI 0.60-0.94) suggesting a significantly lower incidence rate in the SLSJ population, mostly in men aged 40-49 and 50-59.

Period effect

Table 2 shows the average age-adjusted and sex-specific incidence rates of ruptured IAs in each 5-year period. No significant change in average incidence rates was noted, except for women during the 1978-82 period where incidence rate was lower than observed during the other periods. Therefore, we may assume that incidence rates of ruptured IAs in SLSJ region remained stable over the 20-year period of the present study.

Location, size and multiplicity of intracranial aneurysms

The site distribution of 406 of the 412 ruptured IA is presented in Table 3. Ruptured IA occurred almost as frequently in anterior cerebral artery (32.8%), internal carotid artery (31.5%) and in middle cerebral artery (29.3%). Vertebrobasilar artery ruptured IA were uncommon (5.2%). Internal carotid artery aneurysms occurred more frequently in females (36.7%) than in males (24.8%) and anterior cerebral artery aneurysms predominated in males (47.8%) compared to females (21.6%).

The size of the ruptured IAs was specified for 300 of the 412 patients. The size distribution was the following: 0-9 mm, 38.3%; 10-24 mm, 57.7%; ≥ 25 mm, 4%.

The multiplicity of IA was specified for 407 patients; 319 (78.4%) had a single aneurysm and 88 (21.6%) had more than one aneurysm. The distribution of multiple IA was as follows: two IAs, 58 patients (14.3%); three IAs, 24 patients (5.9%); four or more IAs, 6 patients (1.4%). Multiple aneurysms were more common in females (60 patients) than in males (28 patients), as reported for familial and non-familial aneurysms.[16]

Among the 412 cases of ruptured IA, we identified 104 hypertensive patients (25.2%); 68 were female (29.1%) and 36

Table 1: Cases and average annual sex-specific incidence rates per 100,000 of ruptured aneurysms in the SLSJ region, 1973-1992 and Helsinki, 1954-1961.

	Saguenay-Lac-Saint-Jean				Helsinki	
Age group	Cases	Rate	95% CI		Cases	Rate
Male						
0-9	0	0.0	–	–	1	0.3
10-19	5	0.9	0.1	1.7	0	0.0
20-29	19	3.6	2.0	5.3	9	3.6
30-39	46	10.5	7.4	13.5	23	9.6
40-49	30	9.4	6.0	12.7	45	20.0
50-59	47	19.2	13.7	24.7	52	29.5
60-69	26	16.0	9.9	22.2	13	14.5
≥70	5	5.2	0.6	9.7	1	2.6
Total	178	6.3	5.4	7.2	144	9.4
Age-adjusted rate		6.2				
Age-adjusted IRR	0.75 (95% CI 0.60-0.94)					
Female						
0-9	0	0.0	–	–	1	0.3
10-19	3	0.6	0.0	1.2	2	0.8
20-29	21	4.2	2.4	5.9	12	4.0
30-39	47	11.0	7.8	14.1	28	9.3
40-49	60	18.6	13.9	23.3	63	20.5
50-59	54	21.3	15.6	26.9	60	22.5
60-69	40	22.4	15.5	29.3	31	17.0
≥70	9	7.2	2.5	11.9	22	16.1
Total	234	8.4	7.3	9.5	219	11.0
Age-adjusted rate		8.1				
Age-adjusted IRR	0.98 (95% CI 0.81-1.18)					
Whole population						
0-9	0	0.0	–		2	0.3
10-19	8	0.7	0.2	1.3	2	0.4
20-29	40	3.9	2.7	5.1	21	3.8
30-39	93	10.7	8.5	12.9	51	9.4
40-49	90	14.0	11.1	16.9	108	20.3
50-59	101	20.3	16.3	24.2	112	25.3
60-69	66	19.4	14.7	24.0	44	16.2
≥70	14	6.3	3.0	9.6	23	13.1
Total	412	7.3	6.6	8.1	363	10.3
Age-adjusted rate		7.2				
Age-adjusted IRR	0.87 (95% CI 0.75-1.00)					

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Table 2: Average age-adjusted incidence rates of ruptured IAs for male and female by 5-year periods.

	Male		Female		Whole population	
Period	**Rate**	**(CI 95%)**	**Rate**	**(CI 95%)**	**Rate**	**(CI 95%)**
1973-1977	8.2	(7.2 - 9.3)	10.5	(9.4 - 11.6)	9.5	(8.7 - 10.2)
1978-1982	7.1	(6.2 - 8.1)	8.1	(7.1 - 9.0)	7.6	(6.9 - 8.3)
1983-1987	8.1	(7.1 - 9.1)	10.9	(9.8 - 12.1)	9.5	(8.8 - 10.3)
1988-1992	7.4	(6.5 - 8.4)	10.2	(9.1 - 11.3)	8.8	(8.1 - 9.6)

Table 3: Location of 406 intracranial aneurysms from SLSJ population compared with earlier series.

	SLSJ		Earlier series*
ARTERY	**Cases**	**%**	**Range (%)**
Anterior cerebral	133	32.8	30.7 - 43.0
Internal carotid	128	32.5	26.0 - 38.3
Middle cerebral	119	29.3	13.4 - 24.0
Vertebrobasilar	21	5.2	3.0 - 13.5
Other	5	1.2	0.0 - 5.4
Total	406	100.0	

*Sahs 1969 (N=2672),[9] Stehbens 1972 (N=5267),[10] Yoshimoto 1978 (N=1080),[11] Andrews 1979 (N=150),[12] Fox 1983 (N=3110),[13] Hishimoto 1985 (N=5211),[14] Kassell 1990 (N=3521)[15]

were male (20.2%). Hypertension was more common in patients over the age of 50 (37.6%) than in younger patients (15.6%). We found no case of polycystic kidney disease, coarctation of the aorta, Ehlers-Danlos syndrome, Marfan's syndrome, collagen deficiency states or fibromuscular dysplasia.

Discussion

The ascertainment of ruptured IA cases depends on the definition used, the diagnostic procedures and accuracy, and the completeness of case finding in the population.[1] In this retrospective study, a source of underestimation was the use of stringent inclusion criteria for diagnosis of ruptured IA. We included definite cases confirmed by angiography, surgery or postmortem examination and excluded possible cases identified by clinical symptoms and signs, abnormal computed tomography or gross blood in the cerebrospinal fluid. Sudden death from SAH secondary to ruptured IA is another source of underestimation since 8 to 15% of patients with intracerebral or SAH usually die before receiving medical care.[1,17,18] This situation is probably similar in the SLSJ region as it is anywhere else; however, the likelihood of missed cases by sudden death in this series was minimized by a high autopsy rate (45%) in the SLSJ region. In other respects, hospital services in the SLSJ region have remained stable and well distributed during the past 20 years, offering high hospitalization rate in all communities and prompt referral to regional center for accurate diagnosis.

Overall adjusted and age-specific incidence rates of ruptured IA reported in this study for the SLSJ population are not significantly different from those reported in the literature. The overall incidence of ruptured IA was 10.3/100,000/year in the clinical series of Pakarinen.[8] Some studies reported higher incidences of IA in Greenland,[19] New Zealand[20] or Finland,[2,21] and lower incidences of IA in Middle East;[22,23] this raised the question of possible racial diffferences in aneurysm incidence[24]. Weir[25] suggested that apparent frequency within different countries may reflect differences based on the age distribution of the population, prevalence of atherosclerosis and hypertension, habits such as diet, tobacco and alcohol intake. A reasonable set of approximations for the developed countries would be that aneurysm ruptures occur at a rate of about 10/100,000/year;[25] this rate increases progressively with age, possibly declining in extreme old age[1].

A younger mean age at rupture was found for women in the SLSJ population as compared with the results of Pakarinen study (46.9 years for men and 54.8 years for women). This apparent higher proportion of young women at time of rupture is explained by a younger age distribution of the SLSJ population as compared with population of the province of Quebec. However, no increase in age-specific incidence rates for the younger age groups was detected.

Large series on location of ruptured IA showed great variation in the proportion at each site of rupture (Table 3). The proportion of IA at anterior cerebral artery site in the SLSJ population is in the range of these previous series of non-familial aneurysms. The site distribution shows more IA in the middle cerebral artery site in our series than earlier series. Also, our study shows a higher proportion of rupture at a larger size than reported by Weir,[25] who found that 62% of 350 ruptured aneurysms were smaller than 11 mm. The frequency of giant aneurysms (≥ 25 mm) is usually between 3% and 5%;[25] we found the same proportion in our population. No excess of hypertension was identified in this aneurysm population; the prevalence of hypertension was 25.2% for all ages instead of 37% in McCormick series.[26]

The main clinical characteristics of familial IAs are a younger age at rupture,[16,27,28] a lower proportion of anterior communicating artery aneurysms[16] and a rupture at a smaller size[16] than in non-familial IAs. In the present study, the proportion of familial cases was 27.2% (112 familial cases among 412 ruptured IA). Despite this very high familial rate, our study fails to reveal any significant increase in age-specific incidence rates, particularly among younger age groups, and we did not observe a low occurrence of anterior cerebral aneurysms or a tendency to rupture at a small size. However, we can neither reject nor support the genetic predisposition hypothesis for IA in the SLSJ population on this sole epidemiological study. The pattern of inheritance of familial intracranial aneurysm has not been established in the literature. Most authors have suggested dominant or multifactorial inheritance with important genetic heterogeneity and variable expression from family to family.[16,27,29,30] If such phenotypic variability

exists in our population, in particular for the age at rupture, it would be less likely to be uncovered by an epidemiological approach such as the one we have used in this study.

In other respects, since very large kinships are common in the SLSJ region, the high familial occurrence of IA observed may be partly explained by accidental aggregation; this hypothesis merits further investigation.

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