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Trends in the Incidence of Transient Ischemic Attacks, Premorbid Risk Factors and the Use of Preventive Treatments in the Population of Dijon, France from 1985 to 2004

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Key Words
Transient ischemic attacks · Risk factors · Epidemiology · Trends

Abstract
Background: We describe the epidemiological trends of transient ischemic attack (TIA) in a 20-year population-based pilot study. ***Methods:*** Trends in the incidence, risk factors and pre-TIA use of preventive treatments for TIA were observed from 1985 to 2004 according to the classic definition in the population of the city of Dijon, France (150,000 inhabitants). ***Results:*** The raw and standardized incidence of TIA were stable over time. We observed a significant increase in the mean age at TIA onset in women only. The prevalence of hypercholesterolemia and diastolic blood pressure ≥90 mm Hg among patients with TIA increased significantly. This contrasts with falls in smoking and in history of previous myocardial infarction. ***Conclusion:*** The stability of classic TIA incidence, despite the rise in the proportion of elderly people, and the increase in the mean age at onset in women may be considered as a medical progress.

Introduction

The historical definition of transient ischemic attack (cerebral deficit lasting less than 24 h without any sequelae) has some limits despite its interest from an epidemiological point of view [1, 2]. Hence, most TIAs last less than 1 h (two thirds of the cases) and the probability that symptoms lasting more than 1 h disappear within 24 h is low (15%) [2]. In addition, the prevalence of ischemic lesions on MRI increases with symptom duration. Consequently, this definition is not useful because it may induce a delay in the treatment of very acute ischemic stroke that needs emergency care.

On the other hand, the prognosis following TIA is relatively poor, whether for TIA recurrence or for full-blown stroke, or death from a cardiac origin [3]. The risk of stroke occurrence is high in the early post-TIA period, between 2.5 and 5% within the first 48 h and between 5 and 10% within the first month [3–8]. This justifies the use of a simple score in order to identify the risk of severity and recurrence [9]. The long-term prognosis following TIA is also poor, with 16% of mortality and 54% of ischemic events in the following 10 years [4].

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So, a new definition, which would be useful in clinical practice, was proposed by the TIA working group: a TIA is a brief neurological dysfunction induced by a focal brain or retinal ischemic lesion, whose symptoms last in general close to 1 h without any infarction on imaging [2].

Therefore, a review of the epidemiological features of TIA diagnosed according to the classic definition is useful before the generalization and the evaluation of the new definition in medical practice.

Several epidemiological studies on TIA have already been published using the WHO definition of TIA [10–13]. However, some of these studies [3, 5] were performed without confirmation by a physician, or concerned out-of-hospital events, or were not in a population having stable economic characteristics. We have run a continuous nonselected population registry of stroke since 1985 to monitor both first-ever stroke and first-ever TIA according to the classic definition over the past 20 years in the population of the city (150,000 inhabitants). The aim of this study was to analyze the trends of incidence, risk factors and pre-TIA use of preventive treatments in TIA from 1985 to 2004.

Material and Methods

Study Area and Population

According of the censuses of 1982, 1990 and 1999, the population of Dijon was 144,818 inhabitants in 1985, 148,628 in 1995 and 152,043 in 2004. The proportion of people at risk of stroke and TIA ≥75 years of age in Dijon increased by 17% from 1985 to 2004, while the proportion of people ≥85 years increased by 51% from 1985 to 2004.

Case Ascertainment

The major advantage of the Stroke Registry of Dijon is its continuous ascertainment since 1985 [12]. The collaboration of numerous investigators was required, from all of the clinical and radiological departments of the University Hospital and the three private hospitals of the city, and also the 250 general practitioners of the city of Dijon and its suburbs allowing an exhaustive ascertainment. All information collected by the various correspondents on a single file with 95 items, written in 1985, was centralized in the Stroke Registry. TIA was defined according to WHO recommendation as a sudden development of signs and symptoms affecting motor, sensory, sensorial and speech, brainstem and cerebellar functions lasting less than 24 h. All subsequent TIAs occurring after 28 days from onset were recorded as recurrent TIA. There was no limit in terms of age, allowing an ascertainment in elderly, in young adults and even in childhood. All patients with possible TIA were assessed face to face in the first 7 days by the 7 study neurologists working in the University Hospital, to confirm the diagnosis of TIA. The median number of days from event to first assessment by a study clinician was 4 (range 2–8).

CT scans were performed in 90% of the cases in 1980 and in 98% of the cases since 1990 while MRI was performed in 15% of the cases since 2000. The median number of days from event to first imaging by a neuroradiologist or a radiologist was 1 (range 1–3) for CT scan and 7 (range 3–12) for MRI. All the CT scans and MRI imaging were reviewed either by a neuroradiologist in 83% of the cases, or by a radiologist in 17% of the cases. Therefore, diagnosis of the cases was validated according to clinical and imaging criteria by experts.

Cerebrovascular Risk Factors

The study neurologists routinely collected, at the TIA onset, classic vascular risk factors [12]: hypertension if ≥160/95 mm Hg before and during stroke onset, diabetes mellitus if glucose level ≥7.8 mmol/l (patients who had been treated with insulin or oral hypoglycemic agents were also considered as diabetics), hypercholesterolemia if total cholesterol level ≥5.7 mmol/l, or triglyceride level ≥1.6 mmol/l before or at TIA onset, smoking (more than 1 cigarette per day, current or former habit), previous myocardial infarction, angina, peripheral vascular disease, atheroma of cervical arteries diagnosed by ultrasound.

Atrial fibrillation was diagnosed on routinely performed electrocardiogram or Holter recordings. Two-dimensional echocardiography (transthoracic or transesophageal cardiography) was performed to detect other cardioembolic sources.

Carotid and vertebral ultrasonography as well as standard blood and urine tests were routinely performed in all the patients whatever their age.

The use of premorbid preventive treatment was noted: treatment of blood hypertension, diabetes, cardiac arrhythmia, and the use of antiplatelet agents and anticoagulants. In 1985, treatment with lipid-lowering drugs was not recorded and is thus not present on file.

Data Processing and Statistical Methods

To measure the incidence rates, the National Institute of Statistics provided census data for 1982, 1990 and 1999 concerning the population in Dijon in 1-year age groups and by sex. For each of the 20 years of the study, the population was then estimated year by year from these censuses by a linear interpolation from 1985 to 1999, then by extrapolation after 1999. The raw incidence rate, the specific rate per age group, and the standardized rate in terms of the world population before and after 85 years of age [12] were calculated per year and according to sex by the use of the direct method with the SEGI 1996 world population. We assumed Poisson distribution for the annual number of events to calculate 95% confidence intervals (CI) for the rates.

The changing trends given in this study were those based on the annual standardized incidence rates for the Dijon population. Incidence trends were also studied in 10-year age groups. Our model was $y = a \exp(bt)$, where y is the incidence and t is the time in years. Regression coefficients were estimated by the least squares method from incidence rates observed for each year. Linear regression was performed to reveal trends in the prevalence of risk factors and medication during the 20-year observation period. Statistical analysis was performed with STATA® 9.0 software.

Table 1. Distribution of standardized incidence rates of first-ever TIA, by 5-year periods, by age and sex

	1985–1989	1990–1994	1994–1999	2000–2004	Average variation in annual incidence	p value[a]	Relative incidence between first and last period	p value[b]
Standardized overall incidence to world population (per 100,000 per year)								
Men	14.31 (10.48–18.15)	23.20 (18.77–27.62)	5.70 (3.57–7.83)	12.25 (9.08–15.41)	–0.032 (–0.137 to 0.072)	0.61	0.99 (0.83–1.17)	0.95
Women	9.47 (6.86–12.09)	12.10 (9.57–14.62)	4.63 (3.02–6.24)	10.25 (7.72–12.77)	–0.012 (–0.086 to 0.062)	0.78	1.17 (0.84–1.63)	0.32
Overall	11.72 (9.46–13.97)	16.97 (14.57–19.37)	5.13 (3.84–6.41)	11.14 (9.18–13.10)	–0.024 (–0.112 to 0.063)	0.64	1.08 (0.78–1.50)	0.48
Standardized overall incidence to world population by age (per 100,000 per year)								
Age ≥85	163.14 (94.97–231.32)	287.21 (202.34–340.88)	106.79 (61.11–152.46)	147.47 (93.80–201.14)	–0.023 (–0.113 to 0.066)	0.66	0.90 (0.71–1.15)	0.72
Age <85	10.96 (8.70–13.21)	15.61 (13.21–18.01)	4.62 (3.33–5.90)	10.45 (8.49–12.42)	–0.024 (–0.112 to 0.064)	0.64	1.12 (0.83–1.52)	0.36
Age <75	9.53 (7.29–11.77)	12.33 (10.01–14.66)	3.78 (2.53–5.03)	8.22 (6.32–10.13)	–0.030 (–0.112 to 0.052)	0.55	0.93 (0.78–1.09)	0.64

[a] Over 20 years.
[b] 1985–1989 vs. 2000–2004.

Results

Distribution of Mean Age of TIA

Over the past 20 years, we have collected 630 cases of TIA. The mean age was 69.1 years (67.5–70.8; 95% CI) in men and 75.7 years (74.3–77.1; 95% CI) in women with a significant difference ($p < 0.01$). Between the first period (1985–1989) and the last one (2000–2004), we observed a significant increase in the mean age at TIA onset, but in women only (61.7 vs. 72.6; $p = 0.05$).

Distribution of Incidence Rates of First-Ever TIA, by 5-Year Periods, by Age and Sex

There was no significant change between the different 5-year periods in both men and women with no significant difference between the two sexes (table 1). We observed a regular increase in the incidence rates of first-ever TIA with age (table 2).

Distribution of Premorbid Risk Factors and Use of Preventive Treatments by 5-Year Period (table 3)

The proportion of hypercholesterolemia among patients with TIA significantly rose from 12.3% in the first period to 33.5% in the last period ($p < 0.01$). This was associated with a significant rise in the prevalence of diastolic blood pressure ≥90 mm Hg: from 52.8 to 69.4% ($p < 0.01$).

In contrast, there was a significant reduction in smoking between these two periods: from 36.3 to 21.5% ($p = 0.02$), and in previous myocardial infarction: from 26.7 to 17.8% ($p = 0.05$).

The other parameters such as a history of blood hypertension, the prevalence of systolic blood pressure at TIA onset ≥160 mm Hg, diabetes, previous TIA or atrial fibrillation, and peripheral vascular disease did not vary significantly between the first and the last periods.

Concerning premorbid medication, the use of antiplatelet agents significantly increased from 6.2% in the first period to 26.7% in the last ($p < 0.01$). This contrasts with the prevalence of treated blood hypertension and the use of anticoagulants for atrial fibrillation, both of which remained unchanged.

Discussion

This population-based registry, maintained continuously over a period of 20 years, has allowed us to observe some major changes in TIA trends, according to the classic definition. The fact that we did not observe any significant changes in the raw incidence of TIA between 1985 and 2004 is in keeping with data observed in Dijon during the same period for first-ever stroke [14]. Our results are in agreement with other studies that observed

Table 2. Age and sex structure of the study populations and crude annual incidence of TIA per 100,000 population

	Men		Women		Men and women	
	n/n at risk	rate (95% CI)	n/n at risk	rate (95% CI)	n/n at risk	rate (95% CI)
1985–1989						
<55	10/54,224	3.69 (1.77–6.78)	5/56,741	1.76 (0.57–4.11)	15/110,964	2.70 (1.51-4.46)
55–65	13/6,146	42.30 (22.53–72.34)	6/7,605	15.78 (5.79–34.35)	19/13,751	27.63 (16.64–43.16)
65–75	17/4,234	80.30 (46.78–128.57)	16/6,003	53.31 (30.47–86.57)	33/10,237	64.47 (44.38–90.54)
75–85	19/2,780	136.69 (82.30–213.46)	30/4,896	122.56 (82.69–174.96)	49/7,676	127.68 (94.46–168.80)
>85	5/711	140.61 (45.65–328.13)	18/1,986	181.29 (107.44–286.51)	23/2,697	170.56 (108.12–255.92)
Total	64/68,094	18.80 (14.48–24.00)	75/77,230	19.42 (15.28–24.35)	139/145,325	19.13 (16.08–22.59)
1990–1994						
<55	13/55,412	4.82 (2.56–8.24)	2/57,128	0.70 (0.08–2.53)	15/111,114	2.70 (1.51–4.45)
55–65	23/5,397	79.83 (50.60–119.78)	11/6,693	32.87 (16.41–58.82)	34/12,455	54.60 (37.81–76.29)
65–75	33/4,503	145.14 (99.91–203.84)	31/6,773	91.54 (62.20–129.93)	64/11,320	113.07 (87.08–144.39)
75–85	35/2,897	258.67 (180.1–359.74)	52/4,869	213.58 (159.51–280.08)	87/7,576	229.68 (183.97–283.32)
>85	15/1,112	372.30 (208.37–614.05)	29/2,258	256 (172.01–368.87)	44/3,064	287.21 (208.68–385.56)
Total	119/69,321	35.10 (29.08–42.00)	125/77,722	32.17 (26.77–38.32)	244/145,529	33.53 (29.46–38.01)
1995–1999						
<55	5/55,412	1.80 (0.59–4.21)	4/60,240	1.33 (0.36–3.40)	9/115,652	1.56 (0.71–2.95)
55–65	3/5,397	11.12 (2.29–32.49)	2/6,046	6.62 (0.80–23.90)	5/11,443	8.74 (2.84–20.39)
65–75	10/4,503	44.41 (21.30–81.68)	12/6,538	36.71 (18.97–64.12)	22/11,041	39.85 (24.97–60.34)
75–85	11/2,897	75.94 (37.91–135.88)	13/5,172	50.27 (26.77–85.96)	24/8,069	59.49 (38.11–88.51)
>85	3/1,112	53.96 (11.13–157.68)	18/2,821	127.61 (75.63–201.69)	21/3,933	106.79 (66.10–163.24)
Total	32/69,321	9.23 (6.31–13.03)	49/80,817	12.13 (8.97–16.03)	81/150,138	10.79 (8.45–13.41)
2000–2004						
<55	12/55,412	4.33 (2.24–7.57)	13/60,240	4.32 (2.30–7.38)	25/115,652	4.32 (2.80–6.38)
55–65	8/5,397	29.65 (12.80–58.41)	7/6,046	23.16 (9.31–47.71)	15/11,443	26.22 (14.67–43.24)
65–75	18/4,503	79.95 (47.38–126.35)	16/6,538	48.94 (27.98–79.48)	34/11,041	61.59 (42.65–86.06)
75–85	26/2,897	179.50 (117.25–263.00)	37/5,172	143.08 (100.74–197.21)	63/8,069	156.15 (119.99–199.79)
>85	3/1,112	53.96 (11.13–157.68)	26/2,821	184.33 (120.41–270.09)	29/3,933	147.47 (98.76–211.79)
Total	67/69,321	19.33 (14.98–24.55)	99/80,817	24.50 (19.91–29.83)	166/150,138	22.11 (18.88–25.74)

no change in TIA incidence [10–12, 15, 16]. In the Oxford study [13], investigators observed a decrease in the incidence of stroke, but no change for TIA. Nevertheless, we noted great variability in TIA incidence according to the period considered, but no significant change in the annual variations in average incidence was detected, despite the increase in the population at risk of TIA.

The incidence of first-ever TIA in Dijon remained lower than that observed in Oxford (51/100,000/year) [13] or in Cincinnati (83/100,000/year) [6], where racial mixes are different (a greater proportion of high-risk black people). Comparisons to other incidence rates must be made with caution, because in Cincinnati, for example, both first-ever and recurrent events were included. Unlike in Dijon, neither Oxford [13] nor Cincinnati [6] included systematic neuroimaging to validate the diagnosis of TIA and their cases were identified retrospectively from inspection records. In Oxford [13], the case ascertainment was continuous only from 1983 to 1984 and from 2002 to 2004 and in Cincinnati [6], the time period of the study was only 1 year.

The stability of TIA incidence in Dijon may be due to the fact that the prevalence of high systolic blood pressure did not decrease, while that of hypercholesterolemia and high diastolic blood pressure at TIA onset significantly rose. This fact may have counterbalanced the decrease in the prevalence of both smoking and previous myocardial infarction. In Dijon, the ratio of CT scans in strokes to those in TIA detection has been stable for 20 years, up to 95% and so, the stability of the incidence of TIA in Dijon during the last 20 years may be due to medical progress, given the increase in the population at risk of TIA, and may reflect the efficiency of vascular preventive therapies

Table 3. Distribution of premorbid risk factors and use of preventive treatments by 5-year periods

	1985–1989 n (%)	1990–1994 n (%)	1994–1999 n (%)	2000–2004 n (%)	trends[a]	p value[a]	p value[b]
Pre-TIA risk factors							
Hypercholesterolemia	18 (12.3)	32 (12.3)	23 (23.7)	64 (33.5)	0.015	0.05	<0.01
History of blood hypertension	86 (58.9)	148 (56.9)	80 (82.4)	107 (56.0)	0.003	0.82	0.59
Systolic blood pressure at stroke onset							
Mean (95% CI)	158.8 (154.6–163.0)	156.1 (152.7–159.5)	151.2 (145.1–157.2)	157.0 (152.6–161.4)	–0.206	0.59	0.55
Proportion ≥160 mm Hg	83 (57.6)	131 (55.0)	60 (65.9)	72 (50.0)	–0.002	0.77	0.19
Diastolic blood pressure at stroke onset							
Proportion ≥90 mm Hg	76 (52.8)	124 (52.1)	62 (68.1)	100 (69.4)	0.013	0.10	<0.01
Smoking	53 (36.3)	64 (24.6)	30 (30.9)	47 (24.6)	–0.006	0.34	0.02
Diabetes	19 (13.0)	32 (12.3)	3 (3.1)	26 (13.6)	–0.001	0.81	0.87
Previous atrial fibrillation	25 (17.1)	74 (28.5)	33 (34.0)	35 (18.3)	0.002	0.86	0.77
Previous myocardial infarction	39 (26.7)	45 (17.3)	21 (21.6)	34 (17.8)	–0.004	0.33	0.05
Peripheral vascular disease	22 (15.1)	16 (6.2)	8 (8.2)	16 (8.4)	–0.004	0.40	0.06
Pre-TIA medication							
Treated blood hypertension							
% for all patients	70 (47.9)	136 (52.3)	73 (75.3)	93 (48.7)	0.005	0.74	0.88
% only for patients with hypertension	70 (81.4)	136 (91.9)	73 (91.2)	93 (86.9)	0.003	0.57	0.29
Antiplatelet agents	9 (6.2)	37 (14.2)	23 (23.7)	51 (26.7)	0.014	0.02	<0.01
Anticoagulants for atrial fibrillation	4 (2.7)	14 (5.4)	9 (9.3)	14 (7.3)	0.004	0.19	0.06

[a] Over 20 years. [b] 1985–1989 vs. 2000–2004.

applied since 1985. The best proof of such a change in preventive management is the rise in the use of antiplatelet drugs, which may have decreased TIA from macroatheroma or lipohyalinosis.

The second positive impact of this primary prevention is the significant increase in the mean age at TIA onset between the first and last period of our study in women but not in men contrary to stroke. It seems that thanks to better cerebrovascular preventive treatment, we have prolonged TIA-free life by several years in women and stroke-free life in both women and men.

The third major result concerns the changes in the vascular risk factors (table 3). We can compare the trends of risk factors in Dijon with those of the Oxford study [13] where the prevalence of hypercholesterolemia, systolic and diastolic hypertension and smoking significantly decreased, whereas the prevalence of diabetes, atrial fibrillation, myocardial infarction and peripheral vascular disease remained stable. The differences observed between these two very similar studies may reflect differences in food habits, the access to prevention and care or environmental factors.

Our study has some interesting points and some limits. There were no changes in the ethnic mix and economic status of the population of Dijon, or in the organization of the health care system during the 20-year-long study. Diagnostic criteria established by the WHO [1] have been strictly applied over the study period to ensure that secular trends in the incidence of stroke were not affected by changes in diagnostic practices or incomplete ascertainment of cases. Other interesting points were the long-term involvement of the same investigators, the same research team during the 20-year period, and the absence of age limits. Moreover, consistency and reliability were ensured by the high percentage of diagnostic investigations performed on each patient. CT plus MRI scans were performed in almost 100% of the patients in Dijon.

In conclusion, classic TIA incidence was stable with time despite the rise in the number of elderly people, and we observed an increase in the mean age at onset in women only. This is due in part to improvements in primary vascular prevention implemented over the 20-year period. This is confirmed by the decrease in the prevalence of hypercholesterolemia, smoking and previous myocar-

dial infarction and by a greater use of antiplatelet agents. Nevertheless, diabetes and high systolic blood pressure remain undertreated. Because of the ageing of the population, we should expect an increase in TIA during the next years, which underlines the need for an even better prevention strategy.

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