Monday Preference in Onset of Ischemic Stroke

Roberto Manfredini, MD, Ilaria Casetta, MD, Ezio Paolino, MD, Olga la Cecilia, MD, Benedetta Boari, MD, Elisa Fallica, MD, Enrico Granieri, MD

The onset of stroke has a specific temporal pattern (1), characterized by a higher frequency in winter and in the mornings. According to a meta-analysis of more than 11,000 patients, an estimated 37% of strokes occurred during morning hours (2). Variability of the day of week has not been extensively investigated, however. To verify a temporal weekly pattern, we reviewed all cases of stroke admitted to our hospital during a 4-year period.

METHODS

Ferrara is a town in northeastern Italy with a population of 150,000. The only hospital is St. Anna Hospital, the teaching hospital for the University of Ferrara. House calls are made by family physicians during the daytime hours and by Emergency Department physicians during nighttime hours and on holidays at no charge to patients. Key physicians, including neurologists and neurosurgeons, are active 24 hours a day.

We ascertained the occurrence of stroke from January 1, 1994, to December 31, 1997. The diagnosis of stroke, which was always made by a neurologist, was defined according to World Health Organization criteria as rapidly developing clinical symptoms or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. In all patients, diagnostic and laboratory investigations included computed tomography (CT), blood tests, 12-lead electrocardiography, chest radiography, carotid duplex imaging, transcranial doppler imaging, cerebral angiography, echocardiography (transthoracic or transesophageal), and assessment of prothrombotic syndromes were done.

We observed 1610 consecutive cases of stroke (987 [61%] men). The mean ($\pm$ SD) age of patients was 70 $\pm$ 12 years. There were 1,395 (87%) ischemic strokes and 315 (13%) hemorraghic strokes. Stroke onset was defined as the earliest time the patient or witness noted definite neurologic symptoms or signs; this information was obtained from patients, their relatives, or bystanders. Precise determination of the day of onset was possible in all cases.

We performed the main statistical analysis using a partial Fourier series, using a least-squares minimization fitting, and fitting a cosine function to the data by means of a regression method using a 168-hour period. Analyses were made using Chronolab software (3). This method selects the harmonic, or the combination of harmonics, that best explains the variance of the data. The percentage of overall variability of the data about the arithmetic mean that is attributable to the fitted rhythmic function estimates goodness of fit; and an F statistic is used to test the hypothesis of zero amplitude. Significance levels were set at $P < 0.05$.

A circaseptan rhythm, with a significant peak on Monday (Figure, Table), was observed for all strokes ($P = 0.012$) and for ischemic strokes ($P = 0.004$). Stratified analyses of selected subgroups (hypertension and diabetes) showed a Monday peak only for nondiabetic patients ($P = 0.04$). For ischemic strokes, the Monday peak was found only for retired patients ($P = 0.03$).

DISCUSSION

Monday seems to be a critical day for the occurrence of acute cardiovascular diseases. A Monday peak in the onset of cardiac arrest has been reported in a series of more than 6000 out-of-hospital cardiac arrests in Seattle (4) and in a cohort of more than 24,000 sudden deaths in Berlin (5). As there is no evidence of weekly variations for life-threatening ventricular arrhythmias (6), it is possible

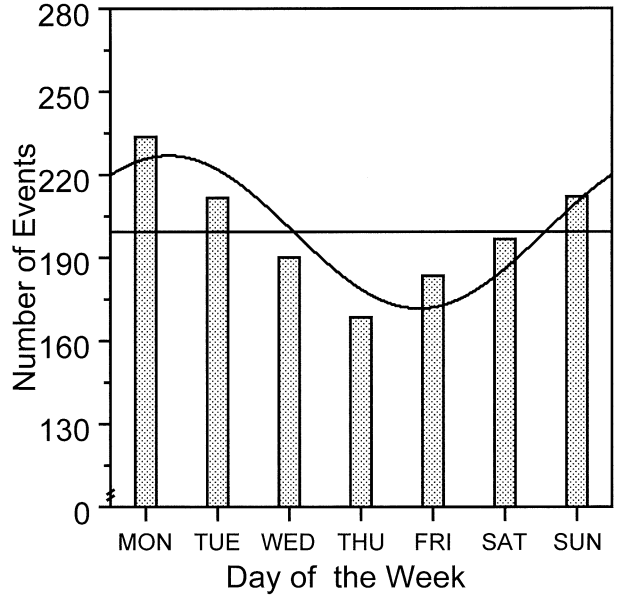

Figure. Weekly variation in the onset of ischemic strokes. Superimposed is the best-fitting curve by Fourier analysis.

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Table. Day-by-Day Distribution of Onset of Stroke, by Sex, Risk Factors, Type of Stroke, and Work Status

	n	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
All strokes	1610	261	236	218	194	223	231	247
Men	987	160	145	142	130	123	145	142
Women	623	101	91	76	64	100	86	105
Hypertension	959	136	143	135	122	129	145	149
Normotension	651	125	93	83	72	94	86	98
Diabetes	346	48	40	39	54	49	50	66
No diabetes	1264	213	196	179	140	174	181	181
Hemorrhagic stroke	215	27	26	28	26	40	34	34
Ischemic stroke	1395	234	210	190	168	183	197	213
Active workers	296	54	34	32	43	47	44	42
Retired	1099	180	176	158	125	136	153	171

that sudden deaths on Monday may be attributable mainly to coronary artery disease. Among Scottish men and women under 50 years of age, mortality from coronary artery disease was about 20% higher on Mondays than on other days of the week (7). Increased mortality from cardiovascular diseases has been observed in Lithuania throughout the weekend and on Monday (8), perhaps due to alcohol use. Two previous studies (9,10) reported about a 20% increase on Mondays in the occurrence of myocardial infarction.

Data from a Norwegian study (11) suggested that biochemical factors associated with cardiovascular risk—such as measures of hematosis and carbohydrate and lipid metabolism—were less favorable on Mondays compared with other days of the week. Thus, similar to the association between increased thrombophilia in the mornings (12,13) and the circadian pattern of other thrombotic disease such as myocardial infarction (14) and limb ischemia (15), the Monday risk of ischemic stroke may reflect an increased thrombogenic condition. On the other hand, in other cardiovascular diseases that have a well-defined circadian pattern (16–19), emotional stress and greater blood pressure may be important factors (20,21).

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REFERENCES

1. Manfredini R, Gallerani M, Portaluppi F, et al. Chronobiological patterns of onset of acute cerebrovascular diseases. *Thromb Res.* 1997;88:451–463.
2. Elliott WJ. Circadian variation in the timing of stroke: a meta-analysis. *Stroke.* 1998;29:992–996.
3. Mojòn A, Fernàndez JR, Hérmida RC. Chronolab: an interactive software package for chronobiologic time series analysis written for the Macintosh computer. *Chronobiol Int.* 1992;9:403–412.
4. Peckova M, Fahrenbruch CE, Cobb LA, Hallstrom AP. Weekly and seasonal variation in the incidence of cardiac arrests. *Am Heart J.* 1999;137:512–515.
5. Arntz HR, Willich SN, Schreiber C, et al. Diurnal, weekly, and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. *Eur Heart J.* 2000;21:315–320.
6. Peters RW, McQuillan S, Gold MR. Interaction of septadian and circadian rhythms in life-threatening ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *Am J Cardiol.* 1999;84:555–557.
7. Evans C, Chalmers J, Capewell S, et al. "I don't like Mondays"—day of week of coronary heart disease deaths in Scotland: study of routinely collected data. *BMJ.* 2000;320:218–219.
8. Chenet L, Britton A, Kalediene R, Petrauskiene J. Daily variations in deaths in Lithuania: the possible contribution of binge drinking. *J Clin Epidemiol*. In press.
9. Willich SN, Löwel H, Lewis M, et al. Weekly variation of acute myocardial infarction: increased Monday risk in the working population. *Circulation.* 1994;90:87–93.
10. Spielberg C, Falkenhahn D, Willich SN, et al. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. *Am Heart J.* 1996;132:579–585.
11. Urdal P, Anderssen SA, Holme I, et al. Monday and non-Monday concentrations of lifestyle-related blood components in the Oslo Diet and Exercise Study. *J Intern Med.* 1998;244:507–513.
12. Brezinski DA, Tofler GH, Muller JE, et al. Morning increase in platelet aggregability. Association with assumption of the upright posture. *Circulation.* 1988;78:35–40.
13. Andreotti F, Davies GJ, Hackett DR, et al. Major circadian fluctuations in fibrinolytic factors and possible relevance to time of onset of myocardial infarction, sudden cardiac death and stroke. *Am J Cardiol.* 1988;62:635–637.
14. Cohen HC, Rohtla KM, Lavery CE, et al. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol.* 1997;79:1512–1516.
15. Manfredini R, Gallerani M, Portaluppi F, et al. Circadian variation in the onset of acute critical limb ischemia. *Thromb Res.* 1998;92:163–169.
16. Gallerani M, Portaluppi F, Grandi E, Manfredini R. Circadian rhythmicity in the occurrence of spontaneous acute dissection and rupture of thoracic aorta. *J Thorac Cardiovasc Surg.* 1997;113:603–604.
17. Manfredini R, Portaluppi F, Zamboni P, et al. Circadian variation in spontaneous rupture of abdominal aorta. *Lancet.* 1999;353:643–644.

18. Gallerani M, Portaluppi F, Maida G, et al. Circadian and circannual rhythmicity in the occurrence of subarachnoid hemorrhage. *Stroke.* 1996;27:1793–1797.
19. Manfredini R, Portaluppi F, Salmi R, et al. Circadian variation in onset of epistaxis: analysis of hospital admissions. *BMJ.* 2000;321: 1112.
20. Gottdiener JS, Krantz DS, Howell RH, et al. Induction of silent myocardial ischemia with mental stress testing: relationship to the triggers of ischemia during daily life activities and to ischemia functional severity. *J Am Coll Cardiol.* 1994;24:1645–1651.
21. Manfredini R, Gallerani M, Portaluppi F, Fersini C. Relationships of the circadian rhythms of thrombotic, ischemic, hemorrhagic, and arrhythmic events to blood pressure rhythms. *Ann NY Acad Sci.* 1996;783:141–158.

From the Department of Clinical and Experimental Medicine (RM, OLC, BB), Section of First Internal Medicine, and the Department of Medical Sciences of Communication and Behavior (IC, EP, EF, EG), Section of Clinical Neurology, University of Ferrara, Ferrara, Italy.

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Correspondence should be addressed to Roberto Manfredini, MD, First Internal Medicine, Department of Clinical and Experimental Medicine, University of Ferrara, via Savonarola 9, I-44100 Ferrara, Italy.

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