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Chronoepidemiology in human diseases

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Summary. - Current knowledges about time-dependent variations in onset of several acute medical diseases are briefly reviewed. Moreover, temporal variation in relative risk factors are also discussed. Any clue to the increased likelihood of a given event can heighten suspicion and shorten time of effective action. The predictability of a certain event, due to the periodicity of cyclic changes, can be of a practical interest in everyday medical practice.
Key words: chronoepidemiology, human diseases.

Riassunto (*Cronoepidemiologia delle patologie umane*). - Gli Autori rivedono brevemente le attuali conoscenze sulle variazioni temporali nell'insorgenza di alcune patologie acute di carattere internistico. Vengono, inoltre, analizzate le relative modificazioni temporali a carico di alcuni fra i principali fattori di rischio. Tali conoscenze possono avere una utile ricaduta sul piano pratico quando si consideri che la possibilità di potere in qualche modo prevedere l'insorgenza di un determinato evento può contribuire sia all'innalzamento della soglia d'allarme sia ad una più tempestiva azione terapeutica.
Parole chiave: cronoepidemiologia, patologie umane.

Introduction

Epidemiology enables us to define numerous conditions which are called "risk factors" because of their association with the development of given diseases. According to risk factors it has been possible to compute the expectation and predictability of the onset of a given disease. The present concept of risk factor is totally dissociated from the possibility that the risk may have a temporal occurrence. Presently, the risk in medicine is linked to the concept of quantity in the sense that it becomes deterministic if its quantitative expression is altered. But in mere terms of quantity, some clinical manifestations of risk are not understandable because there is not an algebraic rule which can be recognized.

The temporal approach to epidemiology, namely the "chronoepidemiology", enabled Tarquini *et al.* [1] to define the concept of "chronorisk", i.e. the risk which shows a systematic periodicity in its time of occurrence. According to these authors, the temporal risk refers to the temporal concomitance of the oscillatory events for the factors which are known to play a role in the pathogenesis, in this case, of atherosclerosis [1].

The risk was due to the summation effects despite the risk factors are normal in the quantitative expression.

In a wider conceptualization, the chronorisk may be, however, seen as "the risk which shows a systematic periodicity in its time of occurrence". This risk is important for epidemiology as the temporal prevalence of a given disease is not implicitly indicative of a systematic periodicity. The systematicity can be ascertained by demonstrating that the temporal variation has a period in which the oscillation has a significant probability of rejecting the null hypothesis of zero amplitude.

With these concepts in mind, a review of these diseases, for which a chronorisk has been demonstrated, is presented herein. Stressing that the most suitable procedures for the chronoepidemiologic estimates are the periodic regression analysis called single cosinor [2-4] and spectral analysis [4, 5] which can be applied to both morbility and mortality due to given diseases.

A detailed synopsis is primarily presented in Table 1.

Cardiovascular and cerebrovascular diseases

Before detailing the findings of chronoepidemiological studies it must be stressed that the main body of literature deals with circadian prevalence of human diseases. Therefore, the presentation will be prominently and briefly based on circadian chronoepidemiology.

Circadian periodicity

Circadian variations have been observed for a number of hemodynamic and cardiovascular parameters including heart rate, systemic blood pressure, coronary artery blood flow, cardiac output,

Table 1. - Human disease for which it has been demonstrated a systematic recursivity in their manifestation. This small sample of the available literature is by no means meant to be comprehensive or complete

	Frequency domain		
	Circadian	Circannual	Other
Cardiovascular diseases			
General	36 38 41 43 44 50		137
Hypertension crisis	35 138-141		
Cardiac arrhythmias	26-33		142
Anginal attacks	35-37 39 40 42-47 143		35
Miocardial infarction	35 48-56 144	145 146	144
Sudden death	50 58-63 86 147	148 86 146	
Pulmonary edema	35 69		
Pulmonary emboli	35 64-66	65-67	
Cerebrovascular diseases			
General	14 70 72 74 75 77 88 91	75 86-88 90 91 95	
Ischemic stroke	70-80 91	75 79 84 87 90 91 94	70 74
Hemorrhagic stroke	70 75 89	75 89	70
Epilepsy	97-108	97 101 107	
Affectives disorders	118-126		
Parasuicide	133 134 136	134 136	
Opiate overdose	128 129	128	
Peptic ulcers	109-111 113	114	115
Gastrointestinal bleeding	116 117	116	
Renal stone colic	149		
Immunological diseases and allergy	150-154	84 153	153
Death by			
All causes	82-86 155	85 86 88 155 156	137 146 157
Cardiac causes	84	85 86	
Ischemic heart diseases	85 86	86 152 158	
Cancers	159	85 160	
Infectious diseases	85	84	
Acute intoxication		85 86	
Paediatric death	84	148	
Suicides	132 134 135	85 86 134	134

peripheral vascular resistances [6-10]. In addition, circadian variations in platelet response to aggregating stimuli, i.e. plasma fibrinogen, coagulation factors concentration, and intrinsic fibrinolytic activity, as determined primarily by inhibitors of plasminogen activation, have been observed [11-23]. All these data seem to indicate a transient risk state of increased coagulability during the morning hours, which can be combined with the circadian elevation of catecholamines [22-25]. The observed periodicities in thrombogenic capacity and vasoactive events seem to correlate, suggesting a mechanism of interaction for which there is the possibility of a summation of effects leading to hypercoagulability, as demonstrated by Tarquini *et al.* [1].

Most of these mechanisms may be taken into account when dealing with cardio-cerebrovascular chronoepidemiology.

Cardiac arrhythmias

Ventricular premature beats [26], and episodes of non-sustained [27] or sustained [28-30] ventricular tachycardia appear to begin most frequently during the awake hours and only rarely during sleep [28, 31, 32]. The sustained supraventricular tachyarrhythmias vary with the time of day, showing nearly equal peaks in the morning and the evening, and trough at night [33, 34].

Life threatening arrhythmias appear to have the highest risk time early in the morning [35].

Transient myocardial ischemia

With improved techniques of ambulatory electrocardiographic monitoring it was clearly established that, in the absence of anti-ischemic therapy, most patients with stable angina exhibit episodes of transient myocardial ischemia with ST segment depression during routine out-of-hospital activities. These studies have shown the peak mostly between 06:00 and 12:00, in a strong coincidence with the awakening time and/or the beginning of the routine activities of life [35-47].

Acute myocardial infarction

Objective evidence that myocardial infarction is at least three times more likely to occur in the morning than in the evening was obtained from the MILIS [48-50] and ISAM [51] studies. Their finding was confirmed by a larger number of studies that used onset of pain as a marker of time of myocardial infarction onset [35, 52-54].

Several features of this morning increase in acute myocardial infarction have been recently explored, demonstrating that the temporal characteristic is no longer appreciable in patients advanced in age, affected by diabetes mellitus, smokers, or affected by a prior infarction [55-57].

Sudden cardiac death

In 1987, Muller [50, 58] and Willich [59, 60] demonstrated a prominent circadian rhythm in the onset of sudden cardiac death with the peak from 07:00 to 11:00 and the trough during the night. A subsidiary peak was observed at 15:00 and 16:00.

Pasqualetti *et al.* [61], found in 269 necropsies for sudden cardiac death a circadian rhythm with a peak from midnight to 08:00, and a minimum in the afternoon.

Our research group investigated 610 cases of non-hospitalized subjects who suddenly died and all underwent autopsy. A statistically significant circadian rhythm was found for sudden death due to acute myocardial infarction (crest at 15:20) and to fatal arrhythmias (acrophase at 13:04). These temporal patterns were found to differ according to age, suggesting that the mechanisms vary as a function of the life span [62, 63].

Pulmonary embolism

The occurrence of a circadian chronorisk for pulmonary embolism has been detected by two Italian groups [35, 64]. The evidence was confirmed by our group on two sample patients recruited both outside and inside the hospital [65-68].

Acute pulmonary edema

The highest frequency of acute pulmonary edema was seem at 22:00 with a subsidiary peak ad midnight and 02:00 [35]. Moreover, patients presenting pulmonary edema between 12:00 and 16:00 had a significantly higher incidence of acute myocardial infarction and death compared with patients presenting at other times [69].

Cerebral stroke

The chronoepidemiological characterization of cerebral stroke along the scale of 24 h is difficult because of the impossibility of determining the onset time in sleeping patients. However, assuming that such events have roughly occurred within eight hours before awakening, it has been demonstrated that their prevalence is from 06:00 to 12:00 [70-78].

In a more detailed analysis, our group demonstrated that strokes occur in the morning between 07:00 and 12:00 in at least 35% of cases. Ischemic strokes and transient ischemic attacks were found to have a peak at 11:56 and 12:41 respectively [79, 80].

Hypertensive crisis

The highest frequency of hypertensive crisis was seem at 10:00, and cosinor analysis found a significant circadian acrophase at 15:00. In circannual analysis the highest frequency was detected in January, while the lowest frequency was found in July and August [35].

Mortality

Analysis of human mortality indicates an increased tendency in the morning, and a significant circadian rhythm was found with a maximum from 02:00 to 10:00 [81-84].

Circannual periodicity

A circannual periodicity has been reported for the mortality of cerebrovascular disease [85, 86] and pulmonary embolism [65-68]. Seasonal variations were also found in the occurrence of ischemic cerebrovascular events and in spontaneous intracerebral haemorrhage occurrence [74, 75, 87-91]. In ischemic stroke, the circannual periodicity was seen to show a peak prevailing in October [79].

The seasonal and annual variations in acute cardiovascular and cerebrovascular events may in

some way be related to both coagulation and cardiovascular effects promoted by environmental agents, mainly the meteorological ones [92, 93]. A reflex influence of the coagulative balance to external temperature has been reported [91, 94, 95]. Furthermore, a circannual rhythm, coincident with cold weather, has been shown in both myocardial infarction [96] and cerebrovascular non-embolic events [94, 95]. Hypertensive effects of low temperatures are well known because of the significant negative correlation between environmental temperature and blood pressure, already revealed by a mild surface cooling [96].

Epileptic seizures

With reference to epileptic episodes, Aristotele had already observed that there was a nocturnal prevalence in the manifestation. Studies performed around the turn of this century provided experimental evidence for this finding [97]. Assuming a nocturnal prevalence, a classification for which the epileptic episodes were recognized as matutinal, diurnal and nocturnal as variations of the diffuse and mixed epilepsy has been proposed [98, 99]. The relation between sleep-wake cycle, epileptic episodes and/or epileptiform EEG discharges registered during the intercritic periods, have also been studied [97, 100-103]. To verify the hypothesis of possible circadian synchronizations, several studies have been performed on animal models [104-106].

Studies performed on congenitally epileptic rats showed that the susceptibility to tonic-clonic crises correspond to the lower vigilance levels [105, 106], and the majority of epileptic episodes, in baboon, have been registered in the morning [104]. When the lighting schedule is modified, however, from 12:12 h light-dark cycle to a constant illumination, the susceptibility to epileptic episodes increases along the 24 h [106].

Recent studies of our group confirmed the presence of a circadian rhythmicity in epileptic episodes onset, with an acrophase in the late morning-early afternoon [107, 108]. As far as regards the study of circannual periodicity, these data showed a winter peak for epileptic episodes in the course of a fever [107].

Gastroenterologic diseases

Several gastrointestinal functions show a circadian organization in their physiology (intragastric pH, gastrin, pepsinogen, gastric mithotic index, etc.). Circadian variations in the pharmacodynamic effect of antireceptor H2 drugs have been also described [109-111].

Experimental ulcerogenesis may pathogenetically be time dependent [110, 112, 113]. The seasonal recursivity of the peptic symptomatology has been biometereologically confirmed [114] as well as its relationship with lunar month [115]. A circannual periodicity of Chron's disease has been also demonstrated (Cugini, personal communication).

Preliminary observations in our studies showed a circadian rhythmicity for gastrointestinal tract bleedings with acrophase in late morning-early afternoon hours for lesions both in upper and lower tract of intestine [116], in accordance with Ergun [117].

Psychiatric disorders

The clinical evidence for recursivity in affective illness suggested a chronobiological approach in order to give a biometric support to observational experiences. The insight was also suggested by findings which support the view that alterations in circadian rhythms occur in association with some affective disorders. A phase shift theory is invoked as a pathogenetic moment for endogenous depression. Clinical manifestations of depressive diseases are said to be characteristic of a postmeridian part of the day [118-126].

In a recent study of our group concerning psychiatric admissions to an Emergency Department, a circadian rhythm with a postmeridian acrophase was found in patients affected by anxiety, dysthymic mood, paranoid and bipolar disorders, and major depression [127].

Drug overdose

Recent studies reported an evening acrophase for hospital admissions for drug overdose [128]. Our recent analysis is consistent with previous results, reporting significant acrophases both for total admissions, females and males respectively at 18:17, 18:23 and 18:18 [129].

The evening prevalence may be justified by the social diurnal involvement of humans in routines. However, it is well known that the majority of drug abusers don't limit the use to only one self-administration daily, and a circadian susceptibility of the organism to various drugs has be considered, as demonstrated in humans and animals for ethyl alcohol, opiates, barbiturates [130, 131].

Suicidal behaviour

Only a few studies are available in literature concerning circadian patterns in occurrence of suicide [132] and attempted suicide [133, 134]. Studies from our group reported circadian periodicities both for suicide [135] and attempted suicide [136], with acrophase, respectively, in late morning and in the evening hours. The concomitance of phase with the cyclicity of some psychiatric disorders leads to the hypothesis that an alteration in rhythmicity of important neurotransmitters and their receptors may play a pathogenetic role.

Conclusions

This review reinforces with its bibliography references the importance of temporal criteria in estimating the risk pattern in some clinical conditions.

According to traditional epidemiology there is a binary logic for which the risk exists or not depending on the quantitative variation of its factors. This interpolation is not able to explain why some diseases occur in subjects apparently "risk-free".

From this presentation, we are now aware that this risk may be sustained by time. The time-related risk, "chrono-risk", may be precociously effective before the quantitative alterations can be seen. Therefore, the identification of a temporal risk for a given clinical disease seems to be fundamental for its prevention as the chrono-risk precedes the quantitative risk, and, thus, it can be used in pre-pathology.

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