Environmental Risk Factors for Stroke and Cardiovascular Disease

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Introduction

The environmental neurology approach to diseases is systematic, holistic, and translational. This approach exists practically as long as the field of medicine itself; indeed, Hippocrates (460-370 BC) emphasized environmental factors in his "*Treaty of Water, Air, and Places*" (Hippocrates et al., 2003; Le Moal and Reis, 2011). To define the environment, we adopt words of Albert Einstein "*The environment is everything that isn't me.*" To this notion, we introduce the concept of environmental risk factors. A systematic approach should explore the multiple dimensions of these factors: their nature, sources, carriers, spatiotemporal characteristics, interactions (multicausality), and finally, health impacts (protective/harmless/noxious) (Reis and Roman, 2007).

In the case of stroke, for example, environmental risk factors can be classified in three categories depending on the nature of the risk (or agent), the milieu conveying the agent (e.g., air, water, soil, food), and the affected population (with a special interest for vulnerable population like children, pregnant women, and seniors). Environmental risk factors also have a geographical or spatial dimension (e.g., altitude, climate). In the previous chapter, we investigated the association of air pollution and stroke, as a well-recognized example of the role of the milieu. Here, we will study environmental factors from another point of view: their nature, be it physical, chemical, or biological. The impact of sociopsychological factors like stress and human interaction is considered elsewhere in this book.

Stroke, as a leading cause of mortality and morbidity around the world, is a major issue in the public health field. Neuroepidemiological studies currently underway are exploring all possible causes and risk factors for stroke. Among them, "new" environmental risk factors are being studied, taking into account the famous Hill's criteria (Hill, 1965). Nowadays, "biologically plausible" mechanisms have gained in importance and should be investigated extensively (Causality Meeting, 2016). In this chapter, we focus on some of the major targets and mechanisms underlying the risk factors involved in stroke: the heart, the vascular endothelium (container), and the blood (content).

Physical Environmental Risk Factors for Stroke

Environmental and Occupational Noise

The concern of the biomedical community and regulatory bodies about the cardiovascular impact of noise developed slowly in the 1980s. The health effects on adults of exposure to transport noise (road, air, and rail) were demonstrated first for hypertension and ischemic heart disease (Babisch, 2006). Addressing the impact of noise in stroke is quite recent; the first relevant publications appeared in 2010. Now, several years later, there is an agreement to consider that traffic noise is the second most important environmental risk factor for stroke in urban societies, after air pollution (Münzel et al., 2017). Comparative burden of disease studies have shown that environmental noise is ranked second in terms of disability-adjusted life years lost (DALYs) in Europe (Stansfeld, 2015). Several recent reviews have addressed the epidemiological evidences (Belojević and Paunović, 2016; Basner et al., 2015; Münzel et al., 2014) and the various potential mechanisms involved (Stokholm et al., 2013).

The impact of occupational noise exposure is controversial. No association has been shown between occupational noise exposure and stroke; risk has largely been attributed to lifestyle (Stokholm et al., 2013). However, in 2015 the Swedish Council

on Health Technology Assessment stated that people who are exposed to noise at work "*more often develop stroke over time than people who are not subjected to noise at work*" (Swedish Council on Health Technology Assessment, 2015).

The sources of environmental noise include trains, road traffic, and aircraft. The impact of noise depends on the nature of the source (rail < road < air) (Münzel et al., 2014), its time of occurrence (daytime versus night), its physical characteristics (e.g., intensity, chronic versus acute), and the exposed population (vulnerability related to age).

Epidemiological studies about the relation between noise and stroke are sometimes contradictory. Long-term air pollution increases stroke risk, regardless of concomitant noise pollution (Hoffmann et al., 2015). Moreover, some epidemiological studies have found no associations; for instance, a study in a Danish cohort of individuals aged 50–64 and another in the Swiss national cohort (Huss et al., 2010) found no association between aircraft noise and stroke mortality (cited in Floud et al., 2013). However, in a Danish cohort of 57,053 people, residential road traffic noise exposure was associated with a higher risk (HR) for ischemic stroke: 14% HR per 10 dB higher exposure to noise for all participants and 27% HR per 10 dB higher exposure to noise for participants above 64.5 years. Stroke risk increased in a dose-dependent manner at exposure levels of 60 dB among the oldest participants (Sørensen et al., 2011). A cross-sectional study from six European countries used data from the Hypertension and Environmental Noise near Airports study including 4712 participants with 276 stroke cases. Members of the study population lived near the major airports in London, Amsterdam, Stockholm, Milan, Berlin, and Athens. An association between nighttime average aircraft noise and heart disease/stroke was found (after adjustment for sociodemographic confounders) for participants who had lived in the same place for ≥20 years (odds ratio: 1.25 per 10 dB). The association between 24-h average road traffic noise level and heart disease/stroke was also significant although the association was not adjusted for air pollution (Floud et al., 2013). In a population of 3.6 million people living near Heathrow airport, a study based on hospital admissions and mortality showed a significant excess risk of stroke and CVD. The noise intensity was investigated by grouping daytime aircraft noise and road noise into six categories from ≤51 to >63 dB in increments of 3 dB and nighttime aircraft noise into 5 dB categories (≤50, >50–55, and >55 dB). In multiple adjustment models, the relative risk (RR) for stroke was 1.24 for daytime aircraft noise (>63 dB v ≤51 dB) and 1.29 for nighttime noise (>55 dB v ≤50 dB). The RR of mortality was similar to those for hospital admissions at the higher noise levels. Thus the RR is the highest with high daytime noise levels and nighttime aircraft noise (Hansell et al., 2013). An 2009 U.S. study, recruited 6 million seniors (>65 years) living near one of the 89 largest airports to evaluate the association between airport-related noise and the risk of hospital admission for CVD and heart failure. Despite the study's methodological limitations, a statistically significant association between exposure to aircraft noise and risk of hospitalization for CVDs was shown (Correia et al., 2013).

One explanation of these contradictory results is related to the difficulty to deal with two major confounders, "indoor noise" produced by the neighborhood in a residential area (Tenaillon et al., 2015) and environmental (ambiant) air pollution, as this pollution shares many common sources with environmental noise (Tétreault et al., 2013).

The pathological effects of noise involve many functions: sleep disruption, disautonomic perturbations (e.g., increases of blood pressure and heart rate), stress reactions (release of stress hormone), and increase of oxidative stress, which in turn may result in vascular endothelial dysfunction and arterial hypertension (Münzel et al., 2014).

Altitude, Air Planes, and Erythropoietin

Altitude is a geophysiological condition which impacts all living organisms. Physical and climatological characteristics, decrease of available oxygen, lower atmospheric pressure and lower temperature, more frequent winds, and a larger exposure to solar radiation are determining Life. These conditions vary according to the altitude, low (<2000 m), moderate (2000–2999 m), high (3000–4999 m), and extreme (>5000 m) and also to the latitude.

Adaptation to high-altitude challenges the brain. As hypoxemia can be deleterious for cellular adaptation and survival, the regulatory homeostasis favors all mechanisms related to convective oxygen transport (cardiovascular, respiratory, and hematopoietic functions) that will counteract a possible cellular hypoxia (Petousi and Robbins, 2014). The first adaptive mechanism is hyperventilation which has the quickest effect. An increase in cerebral blood flow up to 31% of values measured at sea level can occur in few days (3–7) of a subject's transition to high altitudes. The return to sea-level base values follows, depending on the degree of the hypoxic stimulus and on the cerebrovascular sensitivity to hypoxia and carbon dioxide (Bor-Seng-Shu et al., 2012). The heart function is modified typically with tachycardia and no change in stroke volume but a slight temporary blood pressure increase. After a few days of adaptation, cardiac output returns to normal (Naeije, 2010). Supply of oxygen is favored by an adaptive release at the tissue level and an increase of the red blood cells (RBC) production. The direct effect of production is an increase of the hematocrit and the blood viscosity. Other factors contribute also to increased coagulability: namely, increases in platelets (mean platelet volume), erythrocyte aggregability, and plasma viscosity (Bor-Seng-Shu et al., 2012; Alper et al., 2009). Protection of the cellular metabolism involves hypoxia-inducible factor(s) (HIFs) (capable of inducing protective metabolites and proteins) (Kumar and Choi, 2015) as well as chemical agents such as nitric oxide (NO), carbon monoxide (CO), eicosanoid products, oxygen-derived free radicals, endothelins, K^+, H^+, and adenosine (Bor-Seng-Shu et al., 2012), and an control of key enzymes (Na-, K-ATPase). Oxygen-derived free radicals and H_2O_2, NO, and oxidized glutathione are the signaling messengers that make Na-, K-ATPase systems "oxygen-sensitive" (Bogdanova et al., 2016).

The number of exposed people varies; thus, more than 140 million people around the globe reside at high altitude (≥3000 m) in Africa (Ethiopian Highlands; Kilimanjaro), Asia (Himalaya Mountains and Tibet), and the American continents (Rocky Mountains and Andes Mountain Range) (Ronen et al., 2014). Two types of population must be distinguished, the native

mountain-born and the sea-level-born people who need to adapt. In fact, altitude stress and its neuro-cardiovascular consequences differ markedly depending on the cerebrovascular regulation and on the capability to adapt.

Impairment of the cerebral autoregulation is the major risk for travelers who rapidly reach altitudes above 2500 m. They may manifest several syndromes: altitude headache (HAH), acute mountain sickness (AMS), high-altitude cerebral oedema (HACO/HACE), and high-altitude pulmonary oedema (HAPO/HAPE) (Wilson et al., 2009; Yanamandra et al., 2014). Although rarely reported, acute stroke is possible during short-term visits to high-altitude regions (Chan et al., 2012). Thus, stroke or stroke-like episodes have been described in association with high altitude for the first time in 1895 (Szawarski et al., 2012). Differential diagnosis must consider cerebral venous thrombosis (Chan et al., 2012) and HACO, which can mimic stroke and provoke deficits; those resolve with the resolution of cerebral oedema (Yanamandra et al., 2014). In case of stroke, an asymptomatic patent foramen ovale should be excluded (Szawarski et al., 2012; Murdoch, 2015).

High-altitude impact during long-term stays (e.g., several months) has been investigated notably among soldiers stationed in the Himalaya Mountains. The relative risk for stroke above altitudes of 3000 m is significantly increased (Jha et al., 2002) by a factor as high as 10-fold (Niaz and Nayyar, 2003); extreme altitudes (over 5000 m) are associated with a 30-fold risk of spontaneous vascular thrombosis (Anand et al., 2001). Polycythaemia is clearly a major risk factor.

The effect of altitude on native populations is a different issue. Several publications (USA, Kashmir, South America, India) have shown that the incident stroke is lower in these populations compared to populations living at sea-level and lower altitudes (Mahajan et al., 2004), to the contrary of a Saudi Arabian study (al Tahan et al., 1998). A study in Cuzco (Peru), located at 3380 m above sea level, showed a crude prevalence ratio of 6.47 per 1000 (cohort of 3246 individuals). The prevalence risk was related to age, polycythemia, high alcohol consumption, residence's area (down-town versus suburban), blood pressure, and increased hematocrit. These two last parameters may vary following altitude (Jaillard et al., 1995). In the large Swiss National Cohort, a clear dose–response relationship between lifetime altitude exposure and mortality was demonstrated: mortality from coronary heart disease and stroke decreased with increases of altitude (22% per 1000 m and 12% per 1000 m, respectively). Switzerland has specific characteristics: altitude of residence between 200 and 2000 m and minimal changes in geographic latitude. However, this study has several limitations related to the methodology and the impossibility of collecting data on individual risk factors (e.g., atherosclerosis). The conclusion, that being born at higher altitude (although the range is not clear) has a protective effect, needs a clear confirmation. Possible physiological explanations could be found: solar radiation and Vit D, less air pollution, genetics, etc. (Faeh et al., 2009). In any case, these studies point to acclimatization, which differs from adaptation, as it is a long-term population-based process, involving both genetic and gene-environmental mechanisms (Petousi and Robbins, 2014). All populations living at high altitude do not show the same acclimatization. For example, at similar high altitudes, Tibetans have significantly lower hemoglobin concentrations than their Andean or Han Chinese immigrants counterparts (Petousi and Robbins, 2014); they also suffer less from chronic mountain sickness (CMS). Stroke risks should likewise be different.

The stroke's risk related to altitude during airplane travel (potentially associated with hypobaric and hypoxic conditions) is low even in patients with symptomatic carotid occlusion (Reynolds et al., 2014). Recently, the incidental risk has been reevaluated; it is now estimated to be 1 stroke in 35,000 flights (Álvarez-Velasco et al., 2016), or less than one in a million passengers (Humaidan et al., 2016). There is no difference between short-haul (<2 h) and long-haul flights (>2 h) for healthy individuals (Reynolds et al., 2014).

The role of blood erythropoietin (Epo) in the adaptation to high-altitude hypoxic exposure in humans led to its use as medicine and doping in competitive sports (Robinson et al., 2006). Epo causes a rise in red cell mass accompanied by elevated hemoglobin concentrations and hematocrit. Its side effects have been documented (Pope et al., 2014).

Climatic and Meteorological Variables: Seasonality and Temperature

In the context of an increasing interest in the health effects of climate change, climate and weather characteristics are now scrutinized as possible risk factors for stroke.

When considering the admission to a hospital or the mortality, the incidence of ischemic stroke seems to be cyclic during the year. Seasonality has been observed worldwide (Chen et al., 2013a) although some studies have reported no seasonality; for instance, a study in Taiwan (Lee et al., 2008). Furthermore, the peak season differs for different countries. In Japan (Takashima stroke register), an excess of ischemic stroke fatality occurs in spring followed by winter (after adjusting for age, gender); the rates are more when compared to during summer (Turin et al., 2009). In the United States, an epidemiological study conducted in the VA hospitals showed that the peak occurrence for ischemic stroke was mid-May, with the lowest occurrence in early December. The authors emphasized that, "Neither the region (i.e., climate) nor the race of the patient substantially modified the seasonal trend" (Oberg et al., 2000). In Melbourne, Australia, ischemic stroke occurrence was significantly higher during spring than summer (incidence rate ratio (IRR) 1.14) (Mao et al., 2015). Peak season was in winter in Hong Kong (Goggins et al., 2012) and in August in Eastern Turkey, with the lowest occurrence in spring (Anlar et al., 2002). Diverse explanations for these patterns have been proposed, including lunar patterns (Mao et al., 2015), rainfalls related to the El Niño Southern Pacific Oscillation (ENSO) (Kintoki Mbala et al., 2016), and in the case of global mortality, relations to air pollution, and meteorological variables (Qian et al., 2010).

The question addressed in a 2010 paper, "What is it with weather and stroke?" (McArthur et al., 2010), remains crucial. Most evidences suggest that cold and hot apparent temperatures (which consider both air temperature and humidity) are associated with stroke mortality, as shown by the eight Large Chinese Cities Study (Chen et al., 2013a). The results show a U-shaped relationship,

with increased risk at extreme high or low temperatures. The potential effect of cold temperature might last more than 2 weeks in contrast to the more immediate effect of hot temperature. However, the burden of stroke mortality is different. In the six large Chinese cities (2007–2013) the stroke burden was caused by cold temperature and was higher in males and seniors (Yang et al., 2016). The same patterns are known for mortality by all causes (Gasparrini et al., 2015; Medina-Ramón et al., 2006). Several subpopulations are particularly susceptible to temperature extremes, for example, patients with atrial fibrillation (Medina-Ramón et al., 2006). The relationship between heat waves and stroke has been addressed by several articles. Heat waves have a strong adverse effect on stroke mortality with an excess mortality of 6%–52% (Chen et al., 2015). A multicity case-only analysis of 50 U.S. cities showed that extremely high-temperature days posed a higher relative stroke mortality risk compared to pneumonia and CVD (Medina-Ramón et al., 2006). Heat wave (with a 2-day lag) is significantly associated with the risk of hospitalization for stroke (odds ratio [OR] 1.173) with more significance for men and over 80 years, in a study conducted in Pennsylvania (Ha et al., 2014). A Chinese study pointed to a clear spatial pattern of stroke mortality during heat waves; the risk was higher in rural areas (Luhe district) compared to the urban area of Nanjing, probably because of a higher vulnerability of the populations; this vulnerability seems to be linked to the socioeconomic level, the air condition availability, the population's age, and the medical facilities' access (Chen et al., 2015). Obviously, further works are needed to assess the real impact of weather (characterized by temperature, humidity, sunshine duration, etc.) on stroke subtypes and pathogenesis (hemorrhagic/stroke, lacunar/atherothrombotic/cardioembolic).

Biological explanations involve complex interactions between endothelium function, vasomotricity, blood pressure, brain demand for oxygen, and change of the quality of blood components (thrombogenic factors) and blood properties (viscosity). For example, cold induces vasoconstriction while heat promotes dilation (Chen et al., 2013a).

Geomagnetic Storms Can Trigger Stroke: A New Environmental Risk Factor

The term "geomagnetic activity" concerns natural variations in the geomagnetic field (Feigin et al., 2014). A geomagnetic storm is a temporary disturbance of the Earth's magnetosphere caused by a solar wind shock wave and/or cloud of magnetic field which interacts with the Earth's magnetic field; these are prominent during the solar maximum phase of the solar cycle. The sun has a solar cycle which averages 11 years in length; at the end of each cycle, the polar magnetic field of the sun reverses. During these cycles, there is an increased solar activity, which generally has a peak in the middle of the solar cycle. During the solar maximun, the increase of sunspots and the solar storms produce the emission of large quantities of electromagnetic and particle radiation. Theses events are known to disrupt technology such as power grids, magnetic compasses, damage satellite microchips and disturb radio and radar transmissions. The solar minimum refers to a relatively low solar activity. This takes place 5–6 years after the solar maximum.

Levels of geomagnetic activity are commonly measured by the Ap Index. Of all locales, Auckland (Feigin et al., 2014) had the most data collected during the solar maximum years, and even had high levels of geomagnetic activity including during 2003, a solar minimum year. Oxfordshire and Melbourne (Feigin et al., 2014) had data collected during solar minimum years only. However, the solar minimum that Oxfordshire data was collected for had high levels of geomagnetic activity. Melbourne (Feigin et al., 2014) data were collected during times of very low geomagnetic activity. The remaining Northern hemisphere cities had more data collected during solar minimum years: Dijon (8 out of the 11 years) and Northern Sweden (12 of the 20 years). Perth had data collected equally over solar maxima and solar minima. It is important to note that data collection for the four cities overlapped during very low levels of geomagnetic activity (1996–1997).

Overall, geomagnetic storms (Ap Index 60+) were associated with a 19% increase in the risk of stroke occurrence (95% CI, 11%–27%). The triggering effect of geomagnetic storms was most evident across the combined group of all strokes in those aged <65 years, increasing stroke risk by >50%: moderate geomagnetic storms (60–99 Ap Index) were associated with a 27% (95% CI, 8%–48%) increased risk of stroke occurrence, strong geomagnetic storms (100–149 Ap Index) with a 52% (95% CI, 19%–92%) increased risk, and severe/extreme geomagnetic storms (Ap Index 150+) with a 52% (95% CI, 19%–94%) increased risk (test for trend, $P < 2 \times 10 - 16$) (Feigin et al., 2014). It will be necessary to evaluate the impact of geomagnetic storm on air pollutants, as some researchers have suggested that they may act together on the brain and cardiovascular system (Stoupel, 2016).

Ionizing Radiations

Ionizing radiation has been assessed as a risk factor for cardiovascular diseases and sometimes for stroke in different exposure's conditions: military usage, occupational settings (miners), medical treatment (radiotherapy), and rarely in usual environmental exposures. Epidemiological studies have confirmed the radiation-related risks of noncancer outcomes. The stroke risk is related to the conditions of the exposure and the dose of the irradiation.

High doses of radiation for specific solid tumors and/or blood cancers (lymphoma and leukemia), involving specific targets (brain, neck, heart) are associated with an excess of deaths (heart disease or stroke) and an increased risk of stroke (Shimizu et al., 2010). The same risk has been shown among atomic bomb survivors in the Japanese survivors cohort. Radiation exposure has been associated with some CVDs, hypertension (Ozasa et al., 2017), and the risk of atherosclerotic disorders (Ozasa et al., 2016).

The cardiovascular effect of lower-radiation doses has recently been assessed. A systematic review and meta-analysis dedicated to moderate- and low-level whole-body ionizing radiation exposure found an excess population risks (mortality) and for all circulatory diseases. The risk ranged from 2.5%/Sv for France to 8.5%/Sv for Russia (Little et al., 2012). Between 1950 and 2003,

the Life Span Study registered about 9600 deaths related to stroke and 8400 related to heart failure in the Japanese cohort of atomic bomb survivors (86,611 members). For stroke, the estimated excess relative risk (ERR) per gray was 9% on the basis of a linear dose–response model. Individual radiation doses have been estimated and ranged from 0 to >3 Gy (86% received <0.2 Gy). The authors concluded that radiation may increase the rates of stroke and heart disease at moderate dose levels (mainly 0.5–2 Gy) although the results below 0.5 Gy were not statistically significant (Shimizu et al., 2010).

Two cohorts of miners bring precise data about occupational irradiation and notably radon. The Wismut cohort uranium mining company in Eastern Germany included 58,987 men from 1946 to 1989; 5141 deaths from heart diseases, and 1742 deaths from CVDs were observed. There was no evidence for mortality from CVDs when the ERR per unit of cumulative exposure to radon in working level months was analyzed (Kreuzer et al., 2010). Canadian authors came to the same conclusion in the Newfoundland fluorspar miners' cohort (2070 miners followed from 1950 to 2001) (Villeneuve et al., 2007). However, there are some data and clues that point to a relation between radiation and premature development of atherosclerosis (Villeneuve and Morrison, 1997; Xu and Cao, 2014; Simonetti et al., 2014).

Chemical Environmental Risk Factors for Stroke

The millennium years (1995–2005) were accompanied by a huge change of the dominant paradigm; environmental risk factors for CVDs had become a new field of research. The purpose was to better analyze and understand the behind-the-scene agents, notably the effects of various metals, chemicals, and obviously air pollution (Navas-Acien et al., 2005). These chemical compounds have been investigated as they are conveyed by multiple milieus, food, air, and water and related to multiple environmental sources and occupational exposures.

Arsenic, a common metal acting as poison and carcinogen, is nowadays considered as a risk factor for CDVs. In a systematic review of the epidemiologic evidence, in general populations, Navas-Acien et al. (2005) showed a significant increase of the RR for stroke which ranged from 0.69 to 1.53. In an occupational population the RR for stroke mortality ranged from 0.30 to 1.33. However, the best evidence has come from Taiwan; arsenic levels in drinking water were found to be associated with CVDs, in particular with stroke, despite methodological limitations. The RR between the highest and the lowest arsenic exposure's categories ranges from 1.19 to 2.69 for stroke. This is consistent with a role for high arsenic exposure in atherosclerosis. This review and a later one (Moon et al., 2012) pointed to the inconclusiveness of the chronic low-dose exposure to arsenic. Risk assessment, based on epidemiological studies (cohort, case-control cross-sectional, and ecological studies) from the United States, Taiwan, Bangladesh, and China, proposes a no-observed-adverse-effect level of 100 µg/L for arsenic in water, equivalent to an iAs dose of 0.009 mg/kg-day (Tsuji et al., 2014).

Cadmium is the second metal studied as risk factor for CVDs. In their 2013 review of cadmium studies, the team of Navas-Acien gave a pooled RR for stroke at 1.18 although the number of studies with stroke outcome was small (Tellez-Plaza et al., 2013a). The mechanisms of cadmium toxicity (data from animals and experimental) involve atherosclerosis (initiation and progression), increased blood pressure, and kidney damage (Tellez-Plaza et al., 2013b).

The third metal considered as a risk factor is lead. With a comparable methodology as that used for arsenic, Navas-Acien et al. (2007) have identified a positive association of lead exposure with the cardiovascular outcomes (included stroke) and obviously hypertension in general and occupational populations. Stroke mortality was higher among workers with the highest number of employment's years, under lead-exposure conditions (Navas-Acien et al., 2007).

For antimony, barium, chromium, nickel, tungsten, uranium, and vanadium, the scarcity of studies and data is insufficient to establish a role (Nigra et al., 2016).

Some organic compounds should also be considered as potential risk factors for stroke, even if reviews or meta-analyses are lacking. The use of pesticides increased significantly the risk of stroke mortality (RR = 1,91) among aerial applicator pilots versus flight instructors (Cantor and Silberman, 1999). Persistent organic pollutants (POPs) such as chlorinated organic compounds (polychlorinated biphenyls, (PCBs), dioxins, and chlorinated pesticides) were shown to increase the CVDs' risk; dioxin exposure is associated with higher risk and mortality for CVD (Chang et al., 2011; Humblet et al., 2008). The RR for stroke was 1.17 among patients discharged from the hospital after stroke (in New York State) and living near a POPs' source (e.g., waste sites) (Shcherbatykh et al., 2005). A hospitalization population-based study from the same team (Sergeev and Carpenter, 2011) confirmed this risk: the RR for stroke with hypertension was 13.4% higher in populations residing in zip codes containing or abutting POPs' environmental sources (RR = 1.134). The Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS) studied background exposure to POPs. Plasma concentrations of 21 POPs (16 PCB congeners 3 organochlorine (OC) pesticides, 1 brominated diphenyl ether (BDE), and octachlorodibenzo-p-dioxin) were measured. During the 5-year of follow-up, 35 participants (among the cohort of 898, aged at baseline over 70) developed hospital-treated stroke. After adjusting for known stroke risk factors, the PIVUS showed that POPs' plasma concentrations significantly predicted the future risk of stroke (Lee et al., 2012).

Biological Environmental Risk Factors for Stroke

Infections and stroke

Although knowledge about the relation between infections and stroke goes back to the 19th century, with the discovery of the major infections' role in stroke (i.e., bacterial meningitis, sepsis, endocarditis), there has been an increasing interest in this topic over the last 25 years (Lindsberg and Grau, 2003). Besides the "classical" tropical infections, pediatric and adult strokes related to "minor" infections gain a greater attention.

In the tropics, the common central nervous system infections associated with stroke are cerebral malaria, Chagas' disease (which is an independent risk factor for stroke in South America), and neurocysticercosis (causing transient ischemic attacks as well as ischemic strokes). Other pathogens can be involved: bacteria (tuberculosis, syphilis, and brucellosis), viruses (hemorrhagic fevers due to arenavirus and flavivirus, Dengue fever, Japanese encephalitis, Nipah virus), HIV (in young Africans), fungi, and parasites. For example, gnathostomiasis is a cause of subarachnoid hemorrhage in south-east Asia (Sanchetee, 2009; Moghtaderi and Alavi-Naini, 2012). There have been several recent reports of clinical stroke cases linked to emerging viruses, such as Ebola and coronaviruses, including severe acute respiratory syndrome and Middle East respiratory syndrome (Bang et al., 2015). The reported frequency of cerebral infarction cases of neurocysticercosis has ranged from 2% to 12%. Extensive reviews are not available and epidemiological data are lacking. One estimation has been proposed but without a proper methodological support; the assertion is that "*Several diseases that are endemic in the tropics, can be responsible for up to 10% of the cases of strokes in adults.*" (Carod-Artal, 2007).

Although the first cases' reports of arterial ischemic stroke (AIS)/acute infantile hemiplegia related to infections issued in the seventies (Roden et al., 1975; Janaki et al., 1975) and though child infections are common, the interest in infectious pediatric strokes had developed recently, probably due to the AIS scarcity (2,4/100,000 US Children per year) (Fullerton et al., 2015). The Vascular Effects of Infection in Pediatric Stroke (VIPS) case control study demonstrated that childhood infections, including varicella zoster virus (VZV), are associated with an increased risk of AIS. Thirty-nine percent of the cases had a parental report of infection in the prior 4 weeks and the adjusted odds ratio (OR) between infection and childhood AIS was 6.5 (95% CI 3.3–13, for infection in the prior week). Based on serological evidences, the VIPS study also showed that recent herpesvirus infections (VZV, Herpes Simplex Virus HSV1, HSV2, EBV, CMV) are associated with an increased risk of AIS among children (29 days to 18 years old). Acute HSV infection (serologies suggestive of *primary* HSV infection) was present in 40% of AIS cases. Neither subjects with past infection nor reactivated cases with latent infection serological evidence were found to be at risk (Elkind et al., 2016). Although the biologic plausibility of a cerebral arteritis induced by VZV infection appears high, the plausibility of the HSV infection's role needs further investigation (Grose, 2016).

The relationship between herpesviruses and stroke has become an important issue because herpesviruses infect a large population: more than 95% of the world's population is infected by the VZV (Nagel and Gilden, 2014). Zoster can be complicated by a VZV vasculopathy (Nagel and Gilden, 2015). A recent systematic review and meta-analysis (Marra et al., 2017) pooled nine studies, published between 2009 and 2016, and found that the relative risk for stroke after a VZV infection was the highest at one postinfection month (RR of 1.78) and decreased progressively to 1.20 after one year. The RR was higher for a herpes zoster ophthalmic episode (RR: 2.05) and remain elevated for one year. The questioning of Borbinha et al. "*Should We Pay More Attention to Varicella Zoster Infection?*" should be probably, answered positively as more than 50% of strokes in young adults are cryptogenic (Borbinha et al., 2016).

Another recent review (Guiraud et al., 2010) has examined the stroke risk related to a large panel of infections in 11 case-controlled and 1 self-controlled case–series studies. The risk of stroke doubled or tripled within the first week after the infection. Thereafter, it decreased slowly, remaining still significant after 3 months. This increased risk exists regardless of the infection site (OR 2.4 for respiratory and OR 1.6 for urinary tract infection) or the agent type (OR 4.4 for bacterial and OR 2.6 for viral infection) when ORs are calculated during the first week.

Since then, new data have been issued. A meta-analysis analyzed the risk of cerebrovascular disease in the presence of IgG for *Chlamydia* pneumonia, showing that *C. pneumoniae* is strongly associated with stroke among patients with large artery atherosclerosis. However, the results (association or not) depended on the serological methods and infection's biomarkers (Chen et al., 2013b). The limits of meta-analyses are illustrated by the opposite results obtained in the case of *Helicobacter pylori*; one study showed that *H. pylori* infection contributes to the risk of ischemic stroke (Wang et al., 2012), the following study refuted it (Yu et al., 2014).

The mechanisms underlying the effects of infection on the cerebral vascular system are complex; there are several interactions and targets are numerous. The vessels can be damaged by the germs (vasculitis-angiitis), or the arterial vessel walls may develop atherosclerotic vascular lesions with inflammatory and prothrombotic alterations leading to thrombosis; embolic mechanisms can be related to infectious heart failure or directly to plasmatic circulating parasites (microembols). The outcomes are ischemic strokes (cerebral infarction) and/or hemorrhages (intracranial, subarachnoid) (Lindsberg and Grau, 2003; Sanchetee, 2009). The mechanisms of immune reactions involved in atherogenesis and the pathogenesis of stroke have also been investigated. An association of increased serum immune complexes (ICs) with stroke incidence was demonstrated. These ICs are the immune response to an acute infection preceding the stroke. *C. pneumoniae* or *Cytomegalovirus* could trigger such an immune response (Tarnacka et al., 2002).

Venomous bites and stings

"*Snake and spider bites, as well as scorpion stings envenoming are neglected diseases affecting millions of people all over the world*". This introductory sentence of Oscar H Del Brutto's article (Del Brutto, 2013) summarizes well the important burden of these issues despite the scarcity of published case reports and the absence of epidemiological studies about the neurological morbidity and mortality (including stroke) of venom exposure. Venoms are concentrates of complex mixtures of toxins targeting the central nervous system, the neuromuscular transmission, the cardiovascular system, and/or the coagulation cascade. Depending on the toxin, intracranial hemorrhage (Indian red scorpion) or ischemic strokes (snake) may occur (Del Brutto and Del Brutto, 2012).

Although the common occurrence of hymenopteran (wasp, bee) stings, primary neurologic manifestations including stroke, are rare. Around a dozen of cases have been published (Kulhari et al., 2016; Rajendiran et al., 2012; Bilir et al., 2013; Schiffman et al., 2004). No pathogenic hypotheses have been proposed.

Conclusions

Besides individual risk factors (nutrition, physical activity, behavior), we have shown that new and well-recognized, environmental risk factors are also related to stroke. Epidemiological investigations are needed to assess their importance. That is the question raised by Hankey in his 2006 publication's title: *"Potential New Risk Factors for Ischemic Stroke: What is Their Potential?"* (Hankey, 2006) although the impacts of air pollution was ignored at that moment. Nowadays, air pollution has become a major "new" environmental risk factor (Feigin et al., 2016). Should we expect the emergence of other new potent environmental risk factors? The environmental health approach is modifying our understanding of the causes of stroke (Boehme et al., 2017). Consequently the classical recommendations and strategies for prevention (Goldstein et al., 2011) have to be improved. Based on these new issues, physicians should better inform their communities and the policy makers about their respective roles and responsibilities. Together, we should act to reduce the impact of amenable environmental risk factors related to human activities, such as air pollution, noise, and chemical exposures.

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