Ischemic Stroke

Subjects: Pathology

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"The term stroke is defined as "…a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH)…", thus comprising an intraluminal obstructive/ischemic and/or wall tear and a lesion mechanism.

Keywords: ischemic stroke ; pathophysiological/damage mechanisms ; endogenous defense activity ; pleiotropic action ; deproteinized ultrafiltrate/hemodialysate compound ; Actovegin®

1. Introduction

Generally, although with nuances mostly depending on the period when a specific study was undertaken, the geographic area examined, and the research methodology applied, a completed stroke is the most prevalent among major neurological conditions[1] and is the second-leading cause of death worldwide[2]. It has a marked potential to generate residual disability[3]; more precisely, "…almost two-thirds of stroke survivors leave hospital with a disability"[4]. These disabilities are quite often severe and/or permanent and account for the largest proportion of total disability-adjusted life years (DALYs), as the "largest contributor to this burden globally"[5], with a consequent socioeconomic impact[6], thus highlighting the severity of the overall impact of strokes**.** Strokes mainly affect the elderly, but "…approximately 10% of strokes occur in patients below 50 years of age"[7]. The increasing frequency of this condition in younger people represents a divergent trend from its global incidence and mortality, which seem to be diminishing[3][6][7].

"More women than men suffer strokes due to the risks of pregnancy, childbirth, and oral contraceptive use before age 30"[7]. Specifically, due to these risks, 从prevails in younger patients and in elderly women, whereas it is more frequent in adult men, until reaching advanced (over 65 years—o.n.) age[8].

The total number of stroke events in the European Union (EU) was 613,148 in 2015 and is estimated to increase to 819,771 in 2035[9], although the incidence and consequent mortality of strokes have had a descending trend since the early 2000s. Considerable differences exist between Eastern and Western Europe concerning the burden of stroke, which is significantly higher in Eastern European countries, including in terms of the specific mortality, which depends on better and faster treatment. This connects to the overall performance of each health care system, which is in turn linked with its level of financing, as well as with the effectiveness of public education campaigns to encourage an emergency response to stroke[9]. Romania ranks first among EU countries in both stroke incidence and mortality[9].

"Stroke is one of the largest problems and clinical-social challenges within neurology and, in general, pathology. This entry briefly reviewed the main pathophysiological mechanisms of ischemic stroke – which represent, at the same time, targets for medical interventions – including those, identified by modern related knowledge, that can be counteracted, at least partially, by a calf blood deproteinized hemodialysate/ultrafiltrate medicine (Actovegin®)".

2. The Main Pathophysiological Mechanism

Regarding the main pathophysiological mechanisms of ischemic stroke targeted in this study, as preliminary considerations, preformed tissues for specific excitability, such as neurons, and most glial and striated muscle cells do not reproduce or replicate after a person is born[10][11]. Under injury conditions (e.g., ischemia in stroke), the central nervous system (CNS) reacts through preformatted pathways, which, for yet unknown reasons, exert active opposition to axonal regrowth and brakes to self-recovery within detrimental evolutive pathways[12].

A CNS insult entails, conditioned by complex, particular and not yet sufficiently deciphered mechanisms, a succession of local and regional damages. However, these damages have wide impacts from the intimate and genic on the body's ensemble and systemic levels, which are classified as primary and secondary (events cascade) lesions[12][13][14][15][16]. Eventually, in total, the primary and secondary lesions contribute to neurological impairment[15].

Some lesion secondary developments overlap and are common for CNS conditions of different causes and partially comprise related biological pathways[17]. “Therefore, the concept of secondary CNS (including brain) injuries has become, especially in the last decades, the basis for developing an array of neuroprotective modern therapies in traumatic, ischemic, and degenerative injuries of the CNS (including both the brain and the spinal cord)”[13]. Thus, the drastic reduction of the cerebral blood flow by a sudden obstruction of predominantly large extracranial (vertebral/basilar, mostly internal, carotid) and/or intracranial (supplying or emerging from the Circle of Willis) arteries or small vessel(s) exposes the brain, the most dependent organ on oxygen metabolic consumption, to ischemia and deprivation of glucose provision. The latter appears to lower the brain tissue resistance to hypoxia; if such a severe interruption lasts more than five minutes without enough flux compensation through collateral circulation variants, it results in irreversible damage and consequent large brain infarction[18][19][20][21]. The occlusion is caused in most cases by thrombosis/thrombus formation in the atherosclerotic plaques (prominent in the vascular lumen(s)), which characterizes atherosclerotic cerebrovascular disease, microatheroma, lipohyalinosis (related to small, deep vessel thromboses, resulting more often in cerebral lacunar infarct lesions), embolism, hemodynamic severe disturbance leading to cerebral hypoperfusion, or, in rarer cases, local inflammatory conditions, like vasculitis[18][21][22]. The atherosclerotic lesions of the vascular walls are also considered to be of inflammatory origin: leukocyte local infiltration, proinflammatory cytokines, and adhesion molecule release, which favor monocyte and T-lymphocyte endothelial adherence and lead to subsequent penetration and maintenance of a continuous inflammatory status[21][23] and/or a systemically infectious origin (*Chlamydia pneumoniae*, Cytomegalovirus, and *Helicobacter pylori*)[23]. Consequently, after blood supply arrest, a succession of extremely complex and intertwined pathophysiological processes begins within seconds[8], both detrimental and as part of the recovery, which may continue for weeks, months, or years, until reaching a clinical-evolutive relative plateau[24]. These processes are emphasized briefly below.

Abrupt and relatively prolonged deprivation of blood flow, i.e., oxygen and energetic (basically, glucose) support, leads to production collapse and drastic shortage, especially of the metabolically produced principal molecular storage and energy provider, ATP, in the most-affected brain tissue. Such severe biochemical injury generates an important amount of direct necrotic cell deaths in the core of the ischemic zone, in part because the membranes’ functional and structural integrity can no longer be sustained. Being energy-dependent, resting and excitation neuronal states, which are both membrane-active processes, are markedly altered, resulting in local still-living cells dying or being at increased risk of dying (although this may be remedied if irrigation is restored sufficiently quickly). This collateral perfusion occurs in the ischemic penumbra of the infarct’s periphery: (1) in neural control disturbance/abolishment of various types and severities and over different directly and/or indirectly connected territories and (2) in enhanced, inappropriate, and detrimental inner bio-pathologic augmented activity with enhanced ATP consumption, which is already diminished[8][17][25].

If the blood flow arrest continues without sufficient collateral flux supply and within cerebrovascular autoregulation[20] or in the peripherally situated ischemic penumbra, further injuries may occur, including, at the intimate level, disturbance of mitochondrial functionality with a consequently imbalanced ratio between pro- and antioxidant factors (including related scavengers) in favor of the former). Oxidative (or nitrosative) stress is mainly generated by the highly enhanced production of reactive oxygen species (ROS), generally associated with depletion but with time-dependent sequential nuances, instead providing a gene-coded transcription-factor-mediated activation of an endogenous-related defense capability. The antioxidant-response elements (AREs) of antioxidants, such as l-c-γ-glutamyl-l-cysteinylglycine (glutathione (GSH)), are highly important[26][32][28][29][30][32][32]. Subsequently, lipid peroxidation, together with phospholipases, also affect the membranes’ integrity. Other critical damage actions of ROS include augmentation of the Ca^{2+} intracellular amount, cytoskeleton, and DNA insults with protein oxidation[33][34], proclivity to secondary misfolding[17], enhanced involvement by gene expression activation of nuclear factor-κβ (NF-κB) of proinflammatory cytokines (chemokines and interleukins) and adhesion molecules (expressed by activated endothelial cells, which attract and stimulate the tissue plasminogen activator (t-PA) and are also considered to have therapeutic capabilities, as recombinant tissue plasminogen activator; rtPA)[35][36], and the stimulation of matrix metalloproteinases (MMPs) and other (metallo) proteases[20][37].

First, soon after ischemia is installed, neutrophils infiltrate (chemotactism) and injure the blood–brain barrier (BBB). A modern, expanded, more complex, and related conceptual structuring is the neurovascular unit that physiologically entails, by cell–cell signaling and interactions, the coordinated and efficacious comprehension and functioning of the BBB location, neurons, microglia, astrocytes, pericytes, endothelial smooth muscle cells, and intrinsic matrix proteins, and which has the adaptive capability to dynamically modify itself according to and within morphological-functional changes during post-stroke partial recovery[39][39]. Subsequently, macrophages and lymphocytes, including T cytotoxic (natural killer; NK) and B types[34], enter the damaged cerebral tissue within the above-mentioned inflammation context. In addition to those already noted, the related primum movens dwells in the signals represented by the modified osmolarity[40] and consistency of the slack post-occlusion blood, addressed to the local endothelial structure and

thrombocytes[35]. Additionally involved in different but interlinked pathophysiological-related sequences are leukotrienes; growth factors; prostaglandins; astrocytes; further cell adhesion molecules, e.g., selectins; intercellular adhesion molecule 1 (ICAM-1); vascular cell adhesion molecule 1 (VCAM-1); and integrins[8][15][20][34], including with and through microglial cells that are resident in the CNS and partially transformed into phagocytes[35]. Different inflammatory pathways, some of which are respiratory[17], are also stimulated by accumulation of necrotic debris in the focal ischemic zone[37][41].

Consequent to hypoxia, the complex pathophysiological context of the ischemic stroke partially and briefly outlined above also entails acidosis, which is metabolically induced in local hypo- or anoxic circumstances, with the accumulation of lactate and hydrogen ions (H^+); the latter stimulates the production of ferrous iron-mediated ROS[8][25][34][36]. The major pathways for cell deaths are apoptosis (type I) and apoptosis-like/anoikis, autophagy (type II), and necrosis (type III)[17][39][42].

”Brain infarction was traditionally considered to be a classic example of liquefactive necrosis”[43] that can supervene quickly and brutally within a few minutes after severe and prolonged brain ischemia in the cerebral tissue, which has low tolerance to hypoxemia, such that necrosis is prone to be augmented by further pathophysiological mechanisms[44] via osmolar overload and consequent osmolysis, especially if suddenly installed[17][40]. However, a similar irreversible outcome, i.e., cell death, may also result following the other linked pathophysiological secondary injury events (summarized above) but more slowly. These latter delayed deadly damages nonetheless offer a time window for the at-risk biological structures to be rescued, at least partially[8], by spontaneous processes (prompt reperfusion, mainly based on efficient collateral blood supply restoration and vessel repermeabilization) and/or interventions. Within a major ischemic stroke, except for the overall successfully achieved (rtPA) thrombolysis, such favorable inner natural evolutions or outcomes usually do not prevail. Thereby, apoptosis and apoptosis-like phenomena also occur, including concomitantly. The former, apoptosis, is the classic pattern of programmed cell death. It often entails the mediated destruction of caspases via its propensity for phagocytosis cells to break up in connection with nuclear condensation. This may run on the intrinsic[8][27][43] mitochondrial pathway based on the release signaling of cytochrome c (a key component in the respiratory chain) and endonuclease G by proteins such as Bad, Bak, Bax, Bid, and Bim and/or those involved in metabolic pathway regulation and membrane lipids. Apoptosis may also involve permeability transition pore openings in the inner membrane components that mainly contribute to the mitochondrial outer membranes permeabilization (MOMP)[34][43][45][46]. Apoptosis targets connected enzymes such as poly-ADP-ribose-polymerase (PARP), which is, with important sex differences in its effects and with consequent nuclear DNA damage and/or exit from the mitochondria, entrance into the intracellular fluid, and continued translocation into the nucleus of the apoptosis-inducing factor (AIF), considered as being caspase-independent[34][47].

The extrinsic pathway is initiated by suicidal molecular signals such as lethal ligands or death ligand trimer, responsible for the ligation to the cell external surface of death receptors, for tumor necrosis factor (TNF)-related apoptosis-inducing ligands (TRAIL), such as tumor necrosis factor α (TNF-α), the human diploid fibroblast (FS-7) cell-line-associated surface antigen, (Fas)/Apoptosis antigen, Apo-1 (Cluster of Differentiation (CD95)), and death receptor 4 (DR4)[8][34][47][48][49][50]. Eventually, all these pathophysiological mechanisms lead to cellular dysfunction. Apoptosis and apoptosis-like forms are relatively different concerning the related changes in the nuclear structure: apoptosis involves “…stage II chromatin condensation into compact figures…”, whereas apoptosis-like involves “…less-compact chromatin condensation” (stage I)[45].

An additional pathway, named anoikis, involves the detachment of cells from the extracellular matrix (ECM)[51], including mainly with “…MMP-induced proteolysis of the neurovascular matrix …”[39]. This may also lead to programed cell death soon after stroke onset, consequent to the BBB deterioration. Specifically, this occurs due to the neurovascular unit’s morphological impairment, and its secondary disfunction regards the signaling of the related inter-cells with their ECM[17][39].

Notably, in brain ischemia, necrosis, and different types of apoptosis/programed cell death, the same neuron may be affected simultaneously by caspases, calpains, and cathepsins[43]."

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