

Etiopathogenesis of Central Nervous System Gliomas

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Abstract

There is much evidence that gliomas are caused by progressive ischemia, followed by increasing and prolonged hypoxia very close to the subventricular zone. In this way, hypoxia on immature glial cells is the primary cause in gliomas genesis. The ischemic process caused by atherosclerosis, anatomical variants of the arteries in the affected area and associated with carcinogenic agents are the harmful factors. While cytotoxic hypoxia triggers a reactive oxygen species (ROS) overproduction in the glial progenitor cells. Consequently, cellular impairment caused by ROS alters the cell cycle phases and provokes genesis of low-grade glioma. Subsequently, its progression causes angiogenesis and higher-grade cancer cells. Then, the vascular recanalization through aspirin is the indicated therapy to reduce the ischemic process by increasing blood flow and oxygen in the affected zone. Therefore, we must fight against the genesis of atherosclerosis and thus decrease the incidence of "neurodegenerative" diseases and cancer.

Keywords: Cerebral atherosclerosis; Progressive ischemia; Prolonged hypoxia; Free radicals; Subventricular zone; Low-grade glioma

Introduction

Glial tumors are the most common group of primary central nervous system (CNS) tumors (81% of all malignant brain tumors) and include astrocytomas, oligodendrogliomas and ependymomas [1-4]. Based on the histological characteristics of astrocytomas, the World Health Organization (WHO) established the following criteria [5-7]: 1) low-grade astrocytomas (Grade I), 2) astrocytomas proper (grade II), 3) anaplastic astrocytomas (grade III), and 4) glioblastoma multiforme (grade IV). The most common glial tumors are glioblastomas multiforme and anaplastic glioma comprising more than 50% and 10% respectively of the total gliomas [1,2,8]. Low-grade astrocytomas account for 40% to 60% of all tumors in the pediatric age [4,5,9], while oligodendrogliomas account for approximately 4% of all brain tumors [10].

The exact cause of gliomas is not known, but it seems plausible that the ischemia and hypoxia [11-13] associated with the influence of environmental and genetic factors [7,11,12,14,15] are related with the development of low-grade gliomas [1,16,17], similar to other tumors of the body [13,18,19]. For this reasons, I decided to analyse the cause of low-grade gliomas in the CNS. That is, because normal glial cells are transformed into gliomas.

Cerebral Atherosclerosis and "Neurodegenerative" Diseases

During the fetal life, as soon as the blood begins to flow through the aorta and its branches, fatty streaks (atherosclerosis grade I to III) [20] appears in different areas of the aorta artery. Pathological changes which begins in the ascending aorta and aortic arch and then with age, a centrifugal and progressive course continues in the rest of the aorta and its branches [11,12,21]. In this way, fatty streaks or some

atheromas (atherosclerosis grade IV) can be found in supraclinoid carotids and circle of Willis into the 30% of cases, in a pediatric population between 1 to 17 years of age (average 4.5 years) [22]. Atheromatous plaques that are evident in individuals about 30 years or more (atherosclerosis grade IV to VI), demonstrated in arteriographic studies [23-25] and autopsy cases [21,26]; as well as in the origin of the carotid and vertebral arteries at the level of the subclavian and innominate arteries [24,26,27].

These atheromatous findings coincide fairly well with the decline in cerebral blood flow, (CBF) (or arterial blood flow) and oxygen and glucose consumption [28,29] in the vascular territory ahead of arterial stenosis, especially in patients with anatomical variants of the arterial tree [30-32], as well as secondary to adhesive arachnoiditis in the chiasmatic cistern [33]. Normally the mitochondria consume the greatest amount (some 85-90%) of oxygen in cells to allow oxidative phosphorylation (OXPHOS), which is the primary metabolic pathway for ATP production [34,35]. But, intracranial atherosclerosis associated with anatomical variants at the circle of Willis [22,30-32], and branches from the supraclinoid carotids and vertebrobasilar system [36-38]; they all cause varying degrees of ischemia (mild, moderate or severe) and little hypoxia (mild hypoxia) in the cerebrum, brainstem and cerebellum [12,22,39-43]. That is, in the intraparenchymal territory of the cortical perforating and lenticulostriate arteries originating from the anterior, middle and posterior cerebral arteries; as well as in the vascular territory of the collateral branches (recurrent arteries of heubner, anterior and posterior choroidal arteries, posterior communicating arteries, anterior cerebellar arteries, circumferential arteries, posterior cerebellar arteries and antero-ventral spinal arteries) and perforating branches originating from the circle of Willis, supraclinoid carotids, basilar artery and vertebral arteries [22,31-33,36-39,42,43]. The subventricular zone (SVZ) of the lateral ventricles (region that contains adult neural stem cells) [44-47] is vascularized by the distal end of the perforating and collateral branches originated from the cortical arteries, supraclinoid carotids and circle of Willis. Therefore, adult SVZ and its immature cells

(neurons and glial cells) in proliferation y migration are very susceptible to damage by ischemia and hypoxia, especially in the walls of the third ventricle in people around 30 years of age or older [48-50]. In this regard, there is doubt about the presence of neural stem cells in the walls of the third ventricle, in people over 30 years of age.

In the adult encephalon, especially in the brainstem, the slow and progressive ischemic process or for short periods of time [51,52] causes the onset of so-called "neurodegenerative" diseases [12,39-42,48,49]. Because the neuronal and glial injury by ischemia, ischemic penumbra and hypoxia (mild degree), triggers a pathophysiological cascade of events as 1) increased glycolysis and reduced prolyl hydroxylase (PHD) activity, 2) inhibition of the Krebs cycle, 3) accumulation of glutamate and aspartate in the extracellular space, 4) generation of free radicals family, constituted by various forms of active oxygen (reactive oxygen species, ROS) or nitrogen (reactive nitrogen species, RNS), 5) followed by oxidative stress, due to the imbalance between ROS (or RNS) and antioxidant defence mechanisms that leads to modifications in intracellular molecules as nucleic acids, lipids and proteins. The brain is one of the major organs affected by ROS, 6) neurodegeneration and 7) finally, neuronal death and atrophy [39,41,51,53-58]. In addition to this, the ischemic process also causes a reduction in the synthesis of endogenous antioxidants as superoxide dismutase (SOD), glutathione peroxidase (GSH), catalase, and coenzyme Q10, among others [57,58]. In humans, the copper/zinc SOD is present in the cytosol, while manganese SOD is present in the mitochondria [58].

On the contrary, the vascular recanalization by means of aspirin can increase arterial blood flow in the ischemic zone in mild to severe degree [12,13] and so, more nutrients, oxygen and exogenous antioxidants (beta carotene, flavonoids, Vit-C, Vit-E and resveratrol, among others) [57,58] can enter to recover the function of ischemic parenchyma. In other words, aspirin and/or some non-steroidal anti-inflammatory drugs (NSAIDs) can prevent the onset of "neurodegenerative" diseases, and through the omental tissue, improve or cure such diseases [39,42,43,49,50,59,60]. Because the omentum produces revascularization in the ischemic area and adjacent zones, and on the other hand, it provides mesenchymal stem cells [33,39,40,50,59,60]. However, to achieve both therapeutic successes, the patient must have a level of hemoglobin in the bloodstream above 13 gr%, in populations at sea level. Besides, it is very important to have good brain activity (intellectual work), associated with moderate and frequent physical exercises.

Genesis of Gliomas in the Encephalon

The etiology of most adult brain and spinal cord gliomas is not well known [1,2,7,17]. But I believe that similar to tumors outside the CNS, [13,61,62] progressive ischemia in moderate to severe degree [12] and by contrast, increasing and prolonged hypoxia (moderate hypoxia to anoxia) [13,35], associated to environmental carcinogens are the cause of gliomas. So, prolonged hypoxia in small areas of the encephalon, both in the white matter and in the SVZ [45,46,63-67] is the primary cause in low-grade gliomas genesis. Astrocytomas and oligodendrogliomas are located in the frontal lobes in 40% of cases and temporal lobes in 29% of cases [68,69], while the ependymomas are usually located along, within or adjacent to the ventricular system, often in the posterior fossa or in the spinal cord. In adults, 60% of the ependymomas are found in the spinal cord, while in children, 90% of these tumors are found in the encephalon, with the majority located in the posterior fossa [7,70].

So that, unlike the conclusions of other researchers [17,64-67,71-76], I believe that the etiopathogenesis of low-grade gliomas is related with decreasing arterial blood flow (mild to severe ischemia) and by contrast, increasing and prolonged hypoxia (hypoxic microenvironment) associated with environmental carcinogens of endogenous and exogenous origin [12,14,41,54,62,77,78]. We currently know that there is a tendency toward a higher incidence of gliomas in highly industrialized countries, where they use ionizing radiation and are exposed to chemicals [78] and moreover, that the female sex hormones play a role in the development of gliomas in women [15]. Then, the immature glial cells originated from the SVZ, in its process of proliferation and migration to the cerebral cortex and gray nuclei [16,17,46,64-67,79] and in a state of prolonged hypoxia [17,35,80], they emit different biochemical responses in order to minimize the progressive damage caused cytotoxic hypoxia. First, ROS generation by the mitochondrial electron transport chain, leading to activation of hypoxia-inducible factor-1 (HIF-1) and HIF-2 through PHD inhibition; [72,80] Second, from a molecular point view, two transcription factors namely HIF-1 alpha and nuclear factor of kappa-light-chain-enhancer of active B cells (NF-kB), are considered as master regulators of tumor cell adaptation to ROS, [34,56-58,81] and Third, weeks or months later, prolonged hypoxia induce chromosomal abnormalities in the endothelial cells and circulating phagocytes through the induction of ROS [73,75,82] and promotes angiogenesis in the tumor microenvironment; [34,76,83,84] observed in tomographic and magnetic resonance studies in gliomas of grade III to IV. I report two clinical cases operated by presenting low-grade astrocytomas [85]. Case 1: A 36 years old man was admitted to the hospital in December 3, 1980. Two months before he presented indifference, hearing very distant voices followed by 4 predominant left tonic-clonic seizures. Left central facial paresis and left hemiparesis (grade 2/5). CT scans and right carotid angiography was normal. With clinical diagnosis of right fronto-temporal irritative lesión, the patient was operated. During surgery we found cerebral edema and abnormal tissue in area 42 and 43. The histological study showed protoplasmatic astrocytoma in grade I-II (Figure 1).

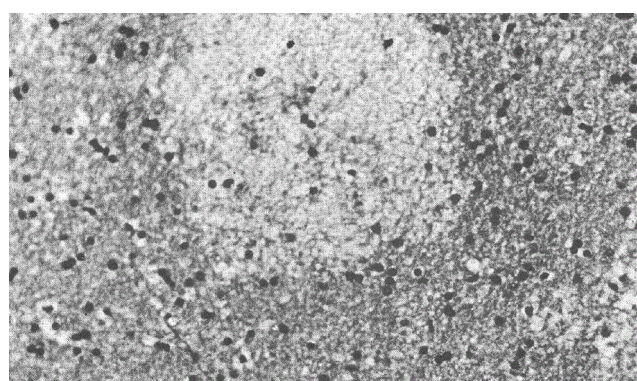


Figure 1: Histological image at medium magnification showing low-grade astrocytoma characterized by astrocyte proliferation, nuclear hyperchromatism and abundant intercellular fibrils [85].

After surgery he received diphenylhydantoin and carbamazepine for one year. The epileptic seizures disappeared. The patient had a 10 years follow-up. Case 2: A 27 years old man was admitted in December 18, 1980. One week before he presented frontal headache, followed by right Jacksonian seizures and then predominant right tonic-clonic

seizures. Right central facial paresis and right hemiparesis. CT scans was normal and left carotid angiography revealed doubtful hypervascularization at the Sylvian triangle. During surgery we found abnormal tissue in area 43 and 44 of Brodmann. Transoperative biopsy was taken in area 43 and then, left prefrontal lobectomy was performed. Histological study showed astrocytoma grade II-III. He received anti-epileptic therapy for 2 years, because the seizures disappeared. The patient had a 8 years follow-up.

On these reported cases, the diagnosis was clinical, because the tomographic and angiographic studies were of little help. Histologically low-grade astrocytomas were characterized by hypercellularity, nuclear hyperchromatism and abundant intercellular fibrils. In some cerebral areas in case 2, there was a marked reaction of endothelium in the blood vessels [85]. For this reason, I agree with other authors that low-grade astrocytomas debut with epileptic seizures and they can be cured with surgery [4,7,10,17,85,86]. For example, according to Suarez et al. [4], in 24 of 30 children operated on by low-grade brain gliomas, they debuted with epilepsy and in 12 patients the tumor was located in the temporal lobe. The genetic studies in all these patients showed no abnormalities.

ROS overproduction is a feature of cancer cells and plays several roles how to react with nucleic acids, lipids, carbohydrates, proteins and the resulting products inducing an imbalance in redox homeostasis [41,57,58,72]. The main linking substances able to relate inflammation to tumorigenesis through the oxidative/nitrosative stress, are prostaglandins and cytokines [61,83]. Therefore, long-term lack of oxygen on immature glial cells is the primary cause in the genesis of gliomas; that is of the uncontrollable growth of glioma cells, expressed as astrocyte proliferation (Figure 1). It is likely that in moderate hypoxia to anoxia, the glycolysis and OXPHOS are reduced until disappear [35,80].

At present, recent research suggest that aspirin use for 6 months or greater is associated with 33% lower gliomas risk compared to those who never took aspirin, probably due to vascular recanalization by aspirin [12]. Because aspirin and NSAIDs inhibit the synthesis of prostaglandin-G2 through the inactivation of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) enzymes, [12,87] and low-dose aspirin is as effective as high-dose aspirin [8,9,87,88]. Besides this, because aspirin is a potent anti-tumoral agent that exerts its anti-neoplastic action by inhibition of the beta-catenin/T cell transcription factor (TcF) signaling pathway in glioma cells; [77] but for this, it is necessary an increase in arterial blood flow [12] in the hypoxic zone, for entrance of aspirin and can exert its action in the hypoxic microenvironment. Therefore, in this way, aspirin reduces or prevents the risk of gliomas genesis, from mature or immature glial cells. In my opinion, in addition to aspirin and NSAIDs, the patient must have a high level of hemoglobin, as well as can be supplemented with hyperbaric oxygenation [89] and/or ozone therapy; because the cancer cells are anaerobic (do not breathe oxygen) and cannot survive in presence of high levels of oxygen [58,76,90,91]. Finally, from the neurosurgical point of view, epileptic seizures caused by ischemia or by low-grade astrocytomas can be reduced or aborted; after revascularization of the epileptogenic focus [33,86,92,93] or removal of the low-grade astrocytoma [4,10,85,94].

Syringomyelia and Ependymomas

The ependymal duct of the spinal cord is covered with simple cubic or cylindrical epithelium with microvelocities and cilia. The cause of

the dilatation of this ependymal conduct or syringomyelia, is not well known [70,95]; but we know that syringomyelia is the development of a fluid-filled cavity or syrinx within the spinal cord. However, based on its anatomical location in the spinal cord and cerebrospinal fluid (CSF) circulation, syringomyelia can be due to 1) syringomyelia with fourth ventricle communication (about 10% of cases); 2) syringomyelia without fourth ventricle communication (about 50% of cases); 3) syringomyelia due to spinal cord trauma (about 10% of cases); 4) syringomyelia associated with spinal dysraphism , 5) syringomyelia due to intramedullary tumors, and 6) idiopathic syringomyelia [69,95,96].

The association between syringomyelia and ependymoma is frequent [89] and however to date, the cause of ependymoma appearance is not fully understood [70,97]. But there are anatomical [98-100] and pathological [101-104] findings that could explain the genesis of syringomyelia such as: 1) location of the ependymal duct within the spinal cord; 2) vascularization of peri-ependymal parenchyma by arterioles and capillaries [99,100]; 3) anatomical variants of spinal cord vascularization [98,99], and 4) degree of dilatation of syringomyelia. Therefore on the basis of the above-mentioned data, I believe that in the zones of greater dilatation there are peri-ependymal zones with varying degrees of ischemia and hypoxia. Thus, hypoxic ependymal cells in moderate to severe degree within the medulla oblongata and spinal cord; they emit response similar to the above-mentioned data for genesis of gliomas. These ependymomas can initially be small, but then grow longitudinally in the ependymal duct, both upward and downward as we show in Figure 2.



Figure 2: Preoperative sagittal T1 MRI scan with contrast showing syringobulbia and solid ependymoma (C4 to C6) and soft ependymoma (C6 to T5) [102].

Therefore, peri-ependymal ischemia is the primary cause of syringomyelia and syringobulbia, while hypoxia in moderate to severe degree causes ependymomas. Both pathologies related to localized atheromatous plaques at the mouths of the vertebral arteries [21,24,27,43], trauma in the spinal cord [96] and anatomical variants of the antero-ventral spinal arteries, postero-lateral spinal arteries, radicular arteries and anterior spinal artery [36,98-100] as well as of circulating environmental chemicals in the bloodstream [11,12,62,82-84].

Conclusion

Consequently, based on the above-mentioned data, ischemia is primary cause of syringomyelia and "neurodegenerative" diseases, while prolonged hypoxia (moderate to severe degree) is responsible of CNS gliomas. First, because hypoxia triggers ROS generation by the mitochondrial electron transport chain, leading to activation of hypoxia-inducible factor-1 (HIF-1) and HIF-2. Second, ROS overproduction causes an imbalance between ROS and endogenous antioxidants leads to modifications in the intracellular molecules and third, this ROS overproduction is a feature of cancer cells and plays several roles during the natural course of malignant tumor. In addition to this, there are exogenous and endogenous risk factors that favor the development of gliomas.

Therefore, the hypoxic microenvironment must be corrected to reduce the risk of generating low-grade gliomas. The increase in arterial blood flow to the hypoxic zone is the indicated procedure. In this regard, several authors report that aspirin and some NSAIDs are the drugs of choice against cell proliferation, because aspirin causes vascular recanalization and thus favors the entry of nutrients, oxygen and inhibits the synthesis of prostaglandins in glial cells. But also, we must avoid being exposed to environmental pollutants to reduce the genesis of atherosclerosis and the entry of carcinogenic agents.

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