ANGIOGENESIS IN PARKINSON'S DISEASE

Y.N. Madjidova¹, *Kh.A. Rasulova¹, S.R. Fakhrgalieva²

Tashkent Pediatric Medical Institute¹, Tashkent, Uzbekistan

Tashkent Medical Academy², Tashkent, Uzbekistan

In the present review, we provide a brief overview of studies on angiogenesis in Parkinson's disease (PD). PD develops from the death of brain cells in a few restricted areas of the brain. The disease was first discovered and its symptoms documented in 1817 (Essay on the Shaking Palsy) by the British physician Dr. James Parkinson; the associated biochemical changes in the brain of patients were identified in the 1960s.

Keywords: Parkinson's disease, angiogenesis, Parkinsonism.

The disease is a progressive movement disorder of the extrapyramidal system, which controls and adjusts communication between neurons in the brain and muscles in the human body. The affected brain cells release dopamine, a chemical messenger that is important for the control of movement, emotional responses and other functions. As the disease progresses, levels of available dopamine fall, and symptoms like tremors, slowness, impaired balance and stiffness get worse. Normal life erodes - at different rates in different people - as walking, talking and looking after oneself become increasingly difficult.

Secondary parkinsonism (or briefly Parkinsonism) is a term used for a symptom constellation that is similar to that of PD but is caused by other disorders or medications. Parkinsonism is a clinical syndrome characterized by tremor, bradykinesia, rigidity, and postural instability [1]. Parkinsonism shares symptoms found in PD, from which it is named; but parkinsonism is a symptom complex, and differs from PD which is a progressive neurodegenerative illness. The underlying causes of parkinsonism are numerous, and diagnosis can be complex [2]. Major reasons for secondary parkinsonism are stroke, encephalitis, narcotics, toxins and carbon monoxide poisoning. There are other idiopathic (of unknown cause) conditions as PD that may cause parkinsonism. In these conditions the problem is not the deficient production of dopamine but the inefficient binding of dopamine to its receptors located on globus pallidus. However, a wide range of other etiologies may

lead to a similar set of symptoms, including some toxins, a few metabolic diseases, and a handful of neurological conditions other than PD [3].

Numerous reviews and articles agree that the exact cause of PD remains unknown. Nowadays there is much evidence of the role of oxidative stress in the development of neurodegenerative diseases, such as PD, Alzheimer disease (AD), Amyotrophic Lateral Sclerosis (ALS) and Huntington's disease (HD). Much of these oxidative damaging processes are associated with an imbalance on the production of ROS that leads to mitochondrial stress and impairment in energy production.

There is no cure for PD, and patients must rely mainly on drug-based treatments to control their symptoms. The drugs are designed to increase dopamine in the affected parts of the brain. Despite adequate medication, many people with Parkinson's disease eventually develop problems with walking and balance. Also, some cannot tolerate full doses of dopamine-restoring medication because of the side effects.

Targeting the formation of unwanted blood vessels in the brain could be a way to help PD patients whose balance and walking difficulties persist despite dopamine-restoring medication.

The formation of new blood vessels, or angiogenesis, in the brain is also a feature of PD and other neurodegenerative disorders. The reason for this is not clear, but one theory is that the death of cells triggers it. Angiogenesis can also be triggered by inflammation and damage to tissue.

*email: khurshidakhon@gmail.com

It is possible to assess the extent of angiogenesis in the brain by measuring biomarkers in cerebrospinal fluid. The most current research was conducted at Lund University in Sweden. In 2015, Dr. Hansson and colleagues found clear links between several markers of angiogenesis and walking or balance difficulties in patients with PD. New research suggests that symptoms associated with PD - including intractable walking and trouble with balance - could be attributed to the formation of unwanted blood vessels - called angiogenesis - in the brain. Despite the use of adequate medication - including dopamine therapy - many PD patients eventually experience some symptoms associated with impaired motor skills. The results are in agreement with other similar research studies, which used brain tissue from deceased patients with PD. According to the study, it has been identified the link between inappropriate angiogenesis and PD symptoms when the researchers made the decisions to take a broader approach to study the mechanisms behind the disease. The measurements showed clear connections between markers of angiogenesis in the brain and walking or balance difficulties among the participants. It was also noted an increased permeability of the blood-brain barrier, which leads to blood components potentially leaking into the brain and causing damage [4].

Patients with PD without dementia displayed higher CSF levels of VEGF, PlGF, and sVEGFR-2, and lower levels of Ang2, compared to controls. Similar alterations in VEGF, PlGF, and Ang2 levels were observed in patients with PD with dementia. Angiogenesis markers were associated with gait difficulties and orthostatic hypotension as well as with more pronounced BBB permeability, WMLs, and CMB. Moreover, higher levels of VEGF and PlGF levels were associated with increased CSF levels of neurofilament light (a marker of neurodegeneration) and monocyte chemoattractant protein-1 (a marker of glial activation). The main results were validated in the 2 additional cohorts. Researchers conclude that CSF biomarkers of angiogenesis are increased in PD, and they are associated with gait difficulties, BBB dysfunction, WMLs, and

CMB. Abnormal angiogenesis may be important in PD pathogenesis and contribute to dopa-resistant symptoms [4].

Angiogenesis, i.e., the formation of blood vessels, has been linked to PD pathogenesis - post mortem analysis of patient's brains has identified increased numbers of nuclei from endothelial cells, blood vessels and increased levels of specific angiogenesis biomarkers. However, angiogenesis' role in PD is not yet completely established and understood. As such, the scientists used biological assays to measure different biomarkers of angiogenesis in CSF samples from PD patients with and without dementia, and compared them to disease-free controls. Additionally, the correlation of these markers' levels with balance problems (a frequent PD symptom), BBB permeability, and brain lesions was also investigated [4].

Brain plasticity is not limited to neurons, but also involves astrocytes and microvascular cells forming so called 'neurovascular unit', which undergo long-lasting functional and structural adaptations in a number of neurological diseases [5]. Endothelial proliferation, angiogenesis and an ensuing transient increase in blood-brain barrier permeability can occur in the adult brain either as an adaptation to locally increased metabolic demands [6,7] or as a response to injury [8,9]. It is therefore not surprising that Faucheux et al. showed an increase in the number of stained nuclei of endothelial cells in the SN of PD patients consistent with an increase in vessel density, but the increase in endothelial cell nuclei was not observed in the ventral tegmental area, an area not affected in PD [9].

Post-mortem investigations on human PD brains and animal models of PD have provided evidence of angiogenesis in the substantia nigra pars compacta [10-13], which have attributed this phenomenon to the ongoing neurodegenerative and neuroinflammatory changes in this region. Barcia and colleagues observed increased numbers of blood vessels in close proximity to degenerating DA neurons in the SN of non-human primates, which correlated with increased VEGF expression [10].

Increasing evidence, however, indicates that the pharmacotherapy of PD may have angiogenic

effects on the brain microvasculature. Strong evidence of treatment-induced angiogenesis has been obtained in rats with unilateral 6-hydroxy-dopamine lesions treated chronically with L-dopa. Animals that develop abnormal involuntary movements in response to L-dopa exhibit endothelial proliferation, upregulation of immature endothelial markers (nestin), downregulation of blood-brain barrier proteins (endothelial barrier antigen) and parenchymal accumulation of albumin in the striatum and its projection targets [14,15]. The angiogenic cytokines mediating endothelial proliferation and microvascular remodelling in this animal model are still unknown and a possible contribution of angiogenesis to the development of LID has not been proven.

Angiogenesis and increased permeability of the blood-brain barrier have been reported to occur in animal models of PD and L-dopa-induced dyskinesia, but the significance of these phenomena has remained unclear. Using a validated rat model of L-dopa-induced dyskinesia, other study demonstrates that chronic treatment with L-dopa dose dependently induces the expression of vascular endothelial growth factor in the basal ganglia nuclei. Findings in the rat model and human patients indicate that vascular endothelial growth factor is implicated in the pathophysiology of L-dopa-induced dyskinesia and emphasize an involvement of the microvascular compartment in the adverse effects of L-dopa pharmacotherapy in PD. This study has provided new evidence about the role and regulation of VEGF in the L-dopa-treated parkinsonian brain. The researchers propose that VEGF-dependent microvascular plasticity contributes to the chronicity of LID in the advanced stages of PD and that it may also contribute to individual variations in the severity of this movement disorder. Protective therapies targeting the vasoactive response to L-dopa may stabilize the

microvasculature and prevent the worsening of dyskinesia over time. Longitudinal studies on patients with PD using a combination of clinical assessments, wet biomarkers and functional imaging approaches will be required to provide definite support for this notion [16].

Research regarding the involvement of the microvasculature in neurological disease is attracting growing interest. Also, two recent in vivo imaging studies have reported blood-brain barrier dysfunction in the midbrain of patients with Parkinson's disease [17]. However, the medication history and therapeutic response to L-dopa were not considered in these investigations.

The presence of $\alpha v \beta 3$ reactive vessels in PD and its syndromes is indicative of newly created vessels that have not likely developed the restrictive properties of the blood brain barrier. Such angiogenic vessels could contribute to neuroinflammation by failing to protect the parenchyma from peripheral immune cells and inflammatory or toxic factors in the peripheral circulation [18].

Many of the cytokines released by activated microglia in PD are not only pro-inflammatory, but are also pro-angiogenic [19,20]. Likewise, the pro-angiogenic molecule, Vascular Endothelial Growth Factor (VEGF) is elevated in the SNpc of PD patients [21].

Angiogenesis may also be associated with blood brain barrier (BBB) dysfunction [22]. In the periphery, newly created angiogenic vessels are leaky due to their numerous fenestrea, widened inter-endothelial junctions, abnormal endothelial cell shape, and discontinuous or absent basement membrane [23].

Thus, angiogenesis has not been fully studied in PD despite being associated with other neurodegenerative disorders. Taken together, these data suggest that angiogenic changes may accompany the pathophysiological processes underlying PD.

REFERENCES

1. Robottom B.J., Weiner W.J., Shulman L.M. "42". International Neurology: A Clinical Approach. Blackwell Publishing.
2. Tuite P.J., Krawczewski K. Parkinsonism: a review-of-systems approach to diagnosis. Seminars in neurology. - 2007. - Vol. 27 (2). 113-22.
3. Christine CW, Aminoff MJ. Clinical differentiation of parkinsonian syndromes: prognostic and therapeutic relevance. Am. J. 2004
4. Janelidze, S., Lindqvist, D., Francardo, V., Hall, S., Zetterberg, H., Blennow, K., Adler, C., Beach, T., Serrano, G., Westen, D., et al. Increased cerebrospinal fluid biomarkers of angiogenesis in Parkinson's disease. Neurology. 2015

5. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. *Trends Neurosci.* 2009;32:421-31.
6. Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, et al. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience.* 2003;117:1037-46.
7. Ding YH, Li J, Zhou Y, Rafols JA, Clark J. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. *Current Neurovasc Res.* 2006;3:15-23.
8. Cavaglia M, Dombrowski SM, Drazba J, Vasanji A, Bokesch PM, Janigro D. Regional variation in brain capillary and vascular response to ischemia. *Brain Res.* 2001;81-93. Nag et al., 2002
9. Faucheux BA, Bonnet AM, Agid Y, Hirsch EC. Blood vessels change in the mesencephalon of patients with Parkinson's disease. *Lancet.* 1999;353:981-2.
10. Barcia C, Bautista V, Sanchez-Bahillo A, Fernandez-Villalba E, Faucheux B, Poza YPM, et al. Changes in vascularization in substantia nigra pars compacta of monkeys rendered parkinsonian. *J Neural Transm.* 2005;112:1237-48.
11. Carvey PM, Zhao CH, Hendey B, Lum H, Trachtenberg J, Desai BS, et al. 6-Hydroxydopamine-induced alterations in blood-brain barrier permeability. *Eur J Neurosci.* 2005;22:1158-68.
12. Wada K, Arai H, Takanashi M, Fukae J, Oizumi H, Yasuda T, et al. Expression levels of vascular endothelial growth factor and its receptors in Parkinson's disease. *Neuroreport.* 2006;17:705-9.
13. Westin JE, Lindgren HS, Gardi J, Nyengaard JR, Brundin P, Mohapel P, et al. Endothelial proliferation and increased blood-brain barrier permeability in the basal ganglia in a rat model of 3,4-dihydroxyphenyl-L-alanine-induced dyskinesia. *J Neurosci.* 2006;26:9448-61.
14. Lindgren HS, Andersson DR, Lagerkvist S, Nissbrandt H, Cenci MA. L-DOPA-induced dopamine efflux in the striatum and the substantia nigra in a rat model of Parkinson's disease: temporal and quantitative relationship to the expression of dyskinesia. *J Neurochem.* 2010;112:1465-76.
15. Ohlin K.E., Francardo V., Lindgren H.S., Sullivan S.E. et al. Vascular endothelial growth factor is upregulated by L-dopa in the parkinsonian brain: implications for the development of dyskinesia / *Brain.* 2011 Aug; 134(8): 2339-2357.
16. Kortekaas R, Leenders KL, van Oostrom JC, Vaalburg W, Bart J, Willemsen AT, et al. Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. *Ann Neurol.* 2005;57:176-9.
17. Bartels AL, Willemsen AT, Kortekaas R, de Jong BM, de Vries R, de Klerk O, et al. Decreased blood-brain barrier P-glycoprotein function in the progression of Parkinson's disease, PSP and MSA. *J Neural Transm.* 2008;115:1001-9.
18. Bradaric B.D., Patel A., Schneider J.A., Carvey P.M., Hendey B. Evidence for Angiogenesis in Parkinson's disease, Incidental Lewy Body disease, and Progressive Supranuclear Palsy. *J Neural Transm.* 2012 Jan; 119(1): 59-71.
19. Naldini A, Carraro F. Role of inflammatory mediators in angiogenesis. *Curr Drug Targets Inflamm Allergy.* 2005;4:3-8.
20. Pogue AI, Lukiw WJ. Angiogenic signaling in Alzheimer's disease. *Neuroreport.* 2004;15:1507-1510.
21. Yasuda T, Fukuda-Tani M, Nihira T, Wada K, Hattori N, Mizuno Y, Mochizuki H. Correlation between levels of pigment epithelium-derived factor and vascular endothelial growth factor in the striatum of patients with Parkinson's disease. *Exp Neurol.* 2007;206:308-317.
22. Barcia C, Emborg ME, Hirsch EC, Herrero MT. Blood vessels and parkinsonism. *Front Biosci.* 2004;9:277-282.
23. Baluk P, Lee CG, Link H, Ator E, Haskell A, Elias JA, McDonald DM. Regulated angiogenesis and vascular regression in mice overexpressing vascular endothelial growth factor in airways. *Am J Pathol.* 2004;165:1071-1085.

XÜLASƏ

PARKINSON XƏSTƏLİYİ ZAMANI ANGIOGENEZ

Məcidova Y.N.¹, Rəsulova X.A.¹, Fəxrəqaliyeva S.R.²

¹*Daşkənd pediatrik tibb institutu, Daşkənd, Özbəkistan;*

²*Daşkənd Tibb Akademiyası, Daşkənd, Özbəkistan*

Təqdim edilmiş məqalədə Parkinson xəstəliyi (PX) zamanı angiogenezin tədqiqatı barədə qısa icmal verilir. Baxmayaraq ki, angiogenez digər neyrodegenerativ xəstəliklər ilə əlaqəlidir, PX zamanı bu problem ətraflı tədqiq edilməmişdir. Əldə edilmiş məlumatlara əsaslanaraq, angiogen dəyişikliklərin PX-nin əsasında duran patofizioloji prosesləri müşayiət etməsi haqda fikir yürütmək olar.

Açar sözlər: Parkinson xəstəliyi, angiogenez, parkinsonizm.

РЕЗЮМЕ

АНГИОГЕНЕЗ ПРИ БОЛЕЗНИ ПАРКИНСОНА

Маджидова Я.Н.¹, Расулова Х.А.¹, Фахргалиева С.Р.²

¹Ташкентский педиатрический медицинский институт, Ташкент, Узбекистан;

²Ташкентская медицинская академия, Ташкент, Узбекистан

В настоящей статье приводится краткий обзор исследований ангиогенеза при болезни Паркинсона (БП). При БП ангиогенез до конца не изучен, несмотря на то, что он связан с другими нейродегенеративными заболеваниями. Данные предполагают, что ангиогенные изменения могут сопровождать патофизиологические процессы, лежащие в основе БП.

Ключевые слова: болезнь Паркинсона, ангиогенез, паркинсонизм.

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