Brain-Derived Neurotrophic Factor

Subjects: Clinical Neurology

Contributor: Eleni Karantali

Brain-derived neurotrophic factor (BDNF) is one of the most studied neurotrophins. Low BDNF concentrations have been noted in patients with traditional cardiovascular disease risk factors and have been associated with the increased risk of stroke/transient ischemic attack (TIA).

stroke BDNF functional outcome acute phase

1. Introduction

Stroke is the second cause of death worldwide and a leading cause of disability [1]. The recent advances in acute ischemic stroke treatment, such as intra-arterial mechanical thrombectomy, improved stroke management and reduced stroke-related disability. Nonetheless, the aging of the population and the increasing prevalence of stroke risk factors are predicted to lead to an increase in stroke survivors. In Europe, the projections forecast a rise of stroke survivors, who will reach the 4,631,050 people in 2035, a 45% increase in stroke-related deaths, and a rise of lost disability-adjusted life years lost (DALYs) by 32% [2]. The need for a potent, non-invasive biomarker which can be used to diagnose and predict the functional outcome of stroke is growing.

Neurotrophins are a family of various soluble molecules, which are involved in multiple nervous system functions, such as cell growth, differentiation, and plasticity [3]. They act through binding to two classes of transmembrane receptors: the tropomyosin-related tyrosine kinase (Trk) receptor family and the p75NT receptor (p75NTR) [4][5]. In the healthy brain, neurotrophins derive from neurons, while peripheral blood cells and cells of the immune system also produce small amounts [3][6]. Their contribution rises when the neurotrophin levels fall due to a pathological CNS process. Brain-derived neurotrophic factor (BDNF) is one of the most studied neurotrophins, the role of which has been unveiled through animal experiments. In the CNS, mature BDNF mediates in synaptic plasticity, dendritic branching, the regulation of both inhibitory and excitatory neurotransmitters, and neuronal growth, while proBDNF contributes to cell apoptosis [4][7][8]. In healthy individuals, BDNF can be detected in the serum and is mostly stored in platelets. The normal values vary depending on the method used [8]. Female individuals have higher levels of BDNF, while a gradual decrease has been reported with increasing age in both sexes. Several studies show that BDNF levels are activity dependent. Physical activity or cognitive enhancement and social activity enhance BDNF expression. On the other hand, a sedentary lifestyle and obesity can lead to decreased concentrations in BDNF [9].

Alterations of BDNF levels in serum have been reported in epilepsy, various neurodegenerative and psychiatric disorders, such as Alzheimer's dementia, and schizophrenia [10]. Low concentrations have also been noted in patients with traditional cerebrovascular disease (CVD) risk factors and metabolic syndrome, while a negative

correlation between circulating BDNF and body mass index, lipid profile and blood pressure has been observed [11]. In a Framingham sub-study, low BDNF levels in healthy individuals were associated with an increased risk of future stroke/TIA [12]. In acute stroke, low BDNF levels have been correlated with worse scores in the National Institute of Health stroke scale (NIHSS), larger infarct volume, and poor long-term functional outcome [13][14].

2. Serum BDNF Levels in Acute Stroke

There is a significant negative association between BDNF and NIHSS; both measured at the acute stroke phase. It is proved that BDNF levels in patients with stroke are significantly increased compared to healthy controls. No association between BDNF and infarct volume was found. We highlighted a potential role of BDNF measured at the acute phase of stroke as a predictor of stroke outcome. In the findings of individual publications studying the role of BDNF-positive PBMCs and Tregs, a correlation with outcome was noted.

BDNF has been extensively used in stroke as an indicator of neural regeneration and recovery. Its role in angiogenesis, neurogenesis, brain repair, and synaptic plasticity has been unveiled through animal experiments and has established BDNF as an important component of post-stroke recovery [8][12][15]. MacLellan has also reported a positive correlation between BDNF and post-stroke rehabilitation in stroke models [16]. Nonetheless, the majority of the studies assessing the utility of BDNF derive from animal experiments. Thus, the exact role of BDNF, specifically in serum, in stroke patients is still unclear.

Stanne reported that BDNF levels measured during the acute stroke phase may not be correlated with early functional recovery (3 months post-stroke), but with late functional recovery (2 and 7 years post-stroke) [17]. The authors accredit their findings to the extended period needed for the recovery of various post-stroke deficits (3 to 6 months after stroke) [18]. From the studies we included, the period from stroke onset to follow-up was heterogeneous. The vast majority conducted a follow-up in less than three months, which varied from a few days post-stroke up to 7 years.

We assessed the role of BDNF levels in serum measured during the acute stroke phase. Di Lazzaro previously reported the stability of serum BDNF during the acute stroke phase in ten patients with first-ever acute ischemic stroke [19]. This finding has been hypothesized to be related to an early increase in BDNF in serum after stroke preceding the blood–brain barrier disruption, which follows at 3-4 h after stroke. In the few studies available with consecutive BDNF measurements after stroke, the findings are conflicting. Rodier studied 40 patients, 24 treated with rtPA, and 14 with standard care [20]. BDNF was measured at day 0, 1, 7, and 90 post-stroke. A variation of BDNF levels was indicated, especially in patients not treated with rtPA. Nonetheless, no available correlation between BDNF values was available to assess whether this variation was significant or not.

Concerning the acute stroke severity, from the twenty-three studies examined, seven studies included patients with mild stroke (NIHSS 1–4), while the vast majority of the studies included patients with mild or moderate stroke (NIHSS up to 15). Only one study included patients with moderate to severe stroke and none with severe. Concurrently, increased stroke severity, and even death by stroke were exclusion criteria in some of the studies

included, especially in some assessing for depression as a primary endpoint. We conclude that the data regarding the utility of BDNF in patients with severe infarcts has not been extensively studied. Nonetheless, both stroke severity, the timing of BDNF measurement after stroke, and all the other study characteristics reported were comparable among the studies we included.

References

1. WHO. The Top 10 Causes of Death. Global Health Estimates; World Health Organization: Geneva, Switzerland, 2020; Available online: (accessed on 29 December 2020).
2. Stroke Alliance for Europe. The Burden of Stroke in Europe; Stroke Alliance for Europe: London, UK, 2017.
3. Sato, C. Releasing Mechanism of Neurotrophic Factors via Polysialic Acid. Vitam. Horm. 2017, 104, 89–112.
4. Lu, B.; Pang, P.T.; Woo, N.H. The Yin and Yang of Neurotrophin Action. Nat. Rev. Neurosci. 2005, 6, 603–614.
5. Berretta, A.; Tzeng, Y.C.; Clarkson, A.N. Post-stroke recovery: The role of activity-dependent release of brain-derived neurotrophic factor. Expert Rev. Neurother. 2014, 14, 1335–1344.
6. Hohlfeld, R. Neurotrophic cross-talk between the nervous and immune systems: Relevance for repair strategies in multiple sclerosis? J. Neurol. Sci. 2008, 265, 93–96.
7. Edelmann, E.; Lessmann, V.; Brigadski, T. Pre- and Postsynaptic Twists in BDNF Secretion and Action in Synaptic Plasticity. Available online: (accessed on 27 November 2019).
8. Panja, D.; Bramham, C.R. BDNF mechanisms in late LTP formation: A synthesis and breakdown. Neuropharmacology 2014, 76, 664–676.
9. Polacchini, A.; Metelli, G.; Francavilla, R.; Baj, G.; Florean, M.; Mascaretti, L.G.; Tongiorgi, E. A method for reproducible measurements of serum BDNF: Comparison of the performance of six commercial assays. Sci. Rep. 2015, 5, 17989.
10. Lima, G.B.; Doorduin, J.; Klein, H.C.; Dierckx, R.A.J.O.; Bromberg, E.; de Vries, E.F.J. Brain-Derived neurotrophic factor in brain disorders: Focus on neuroinflammation. Mol. Neurobiol. 2019, 56, 3295–3312.
11. Golden, E.; Emiliano, A.; Maudsley, S.; Windham, B.G.; Carlson, O.D.; Egan, J.M. Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: Data from the baltimore longitudinal study of aging. PLoS ONE 2010, 5, e10099.
12. Pikula, A.; Beiser, A.S.; Chen, T.C.; Preis, S.R.; Vorgias, D.; Decarli, C. Serum brain-derived neurotrophic factor and vascular endothelial growth factor levels are associated with risk of stroke

and vascular brain injury framingham study. Stroke 2013, 44, 2768–2775.

13. Qiao, H.J.; Li, Z.Z.; Wang, L.M.; Sun, W.; Yu, J.C.; Wang, B. Association of lower serum Brain-derived neurotrophic factor levels with larger infarct volumes in acute ischemic stroke. J. Neuroimmunol. 2017, 307, 69–73.
14. Stanne, T.M.; Aberg, N.D.; Nilsson, S.; Jood, K.; Blomstrand, C.; Andreasson, U. Low circulating acute brain-derived neurotrophic factor levels are associated with poor long-term functional outcome after ischemic stroke. Stroke 2016, 47, 1943–1945.
15. Mamounas, L.A.; Altar, C.A.; Blue, M.E.; Kaplan, D.R.; Tessarollo, L.; Lyons, W.E. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. J. Neurosci. 2000, 20, 771–782.
16. MacLellan, C.L.; Keough, M.B.; Granter-Button, S.; Chernenko, G.A.; Butt, S.; Corbett, D. A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. Neurorehabil. Neural Repair 2011, 25, 740–748.
17. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. The PRISMA Group. PLoS Med. 2009, 6, e1000097.
18. Caplan, L.R. Caplan’s Stroke: A Clinical Approach, 5th ed.; Cambridge University Press: Cambridge, UK, 2016.
19. Di Lazzaro, V.; Profice, P.; Pilato, F.; Dileone, M.; Florio, L.; Tonali, P.A. BDNF plasma levels in acute stroke. Neurosci. Lett. 2007, 422, 128–130.
20. Rodier, M.; Quirié, A.; Prigent-Tessier, A.; Béjot, Y.; Jacquin, A.; Mossiat, C. Relevance of post-stroke circulating BDNF levels as a prognostic biomarker of stroke outcome. Impact of rt-PA treatment. PLoS ONE 2015, 10, e0140668.