Review Article

Clinical usefulness of brain-derived neurotrophic factor in paediatric psychiatry

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Introduction

Many proteins originate from the neurological system[1-5]. Brain derived neurotrophic factor (BDNF) is a neurotrophin, related to the canonical nerve growth factor[1-6]. It has physiological effects on neurons of the central nervous system (CNS) and the peripheral nervous system. Clinically BDNF is altered in many psychological disorders[4]. BDNF plays a role in many clinical psychiatric disorders, including schizophrenia, depression, and autism via a neuro-inflammatory process resulting from several BDNF related signalling pathways[6].

Genetically, BDNF is encoded by the BDNF (also known as BULN2) gene (Gene ID 627) in humans. The specific gene encoding BDNF is at chromosome 11, location 11p14.1. BDNF is first synthesized in the endoplasmic reticulum before it is secreted from dense-core vesicles[7-8]. The genetic polymorphism of BDNF plays a role in its phenotypic association. Considering RNA expression, tissue enhancement is detected in the brain with its highest levels at the cerebral cortex and skeletal muscle. There are expressional levels at lung, liver, kidney, eye and endocrine tissue. In blood, the expression is very low[7]. For protein expression, a medium score is observed in the brain, whereas a low score is observed in thyroid, parathyroid, adrenal gland and sexual organs[7]. There is no protein expression in blood and other tissues[7].

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BDNF is generated by the human neurological system and plays an important role in neurological homeostasis, promoting neuron survival and controlling growth and differentiation of new neurons and synapses. Specific intracellular signalling and changed expression of BDNF are reported in many diseases. Briefly, background genetic factors and external environmental insults play roles as triggering factors resulting in local abnormalities. Regional increase or decrease of DNF expression occurs and further plays a role in phenotypic expression, the clinical presentation (Figure 1). There are applications of BDNF testing in many clinical problems including psychiatric disorders (Table 1). In this review, authors provide insights into the molecular characteristics of BDNF and highlight important details of BDNF laboratory diagnostic tests in clinical paediatric psychiatry.

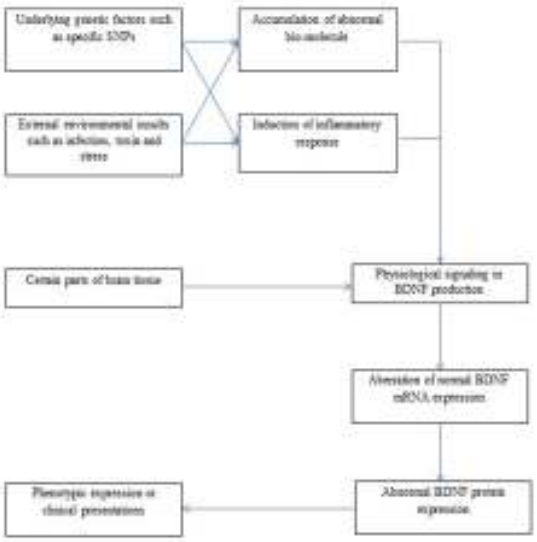

Figure 1: ***BDNF and specific intracellular signalling and changed expression of BDNF in important medical disorders***

Table 1: ***The main effects of BDNF in different medical disorders***

Medical disorder	Summary
Epilepsy	The upregulation of BDNF is observed. Regional increases are detected in temporal lobes. There is an association with epileptic activity. Anticonvulsant therapy results in downregulation. Monitoring of BDNF is a possible useful tool for determining epileptic activity.
Neurodegenerative disease	The downregulation of BDNF is seen at the specific degenerative part of the brain in each neurodegenerative disease. There are specific regional decreases in different neurodegenerative disease (cortex in Alzheimer disease, basal ganglia in Parkinson disease and hippocampus in autism). There is an association between BDNF level and severity of the neuro-deficit. Since there is usually a cellular abnormality that results in deteriorated BDNF in neurodegenerative disease, the BDNF becomes a newly proposed therapeutic alternative for management of the patient.
Psychiatric disorders	Stress can induce downregulation of BDNF. The decreased BDNF level is observed during dysthymia episode. The progression of psychiatric disorder can be assessed by monitoring change in BDNF level.
Infectious disease	Increased BDNF level is observed in some infections such as HIV infection and Zika virus disease. The role of BDNF in infectious disease is limited currently is an issue for further research.

BDNF: Brain derived neurotrophic factor

Psychiatric disorders and BDNF

Schizophrenia

Schizophrenia is an important neuropsychiatric disorder that presents in children and adolescents with a combination of hallucinations, delusions, extremely disordered thinking and behavioural changes[8-11]. The molecular dysfunction in the BDNF signalling pathway, which results in downregulation, is associated with susceptibility to schizophrenia[5,12-13]. The role of BDNF in the pathogenesis of schizophrenia is widely studied. Basically, there is a downregulation of BDNF in the brain of a schizophrenia patient. There is a long-lasting down-regulation of BDNF transcripts III and IV induced by social defeat stress in schizophrenia[13]. Many studies have shown that BDNF is relevant to schizophrenia-related phenotypes[13]. The genetic polymorphism, especially for Val → Met substitution, is widely studied[13,14-17]. Di Carlo P, *et al*[5] concluded that the Val → Met substitution was related to impaired activity-dependent secretion of BDNF and disruption of BDNF signalling was associated with altered synaptic plasticity and neurodevelopment. Nevertheless, Di Carlo P, *et al*[5] noted that genome-wide association studies failed to associate the BDNF locus with schizophrenia. Therefore, the inter-relationship between schizophrenia and BDNF is an interesting issue for further research.

Major depressive disorder

Major depressive disorder is a mood disorder that can be seen in any age group including the paediatric population[17,18]. It can cause a persistent feeling of sadness and loss of interest and it might interfere with daily functioning of the patient[17,18]. The role of BDNF in pathogenesis of major depressive disorder is widely studied. Basically, depressive stress resulted in reduced BDNF expression in the hippocampus and this downregulation of BDNF in the brain is associated with the occurrence of major depressive disorder.

Bipolar disorder

Bipolar disorder is another important psychiatric problem presenting as extreme shifts in mood from depression to mania[19-21]. The role of BDNF in pathogenesis of bipolar disorder is widely studied. In bipolar disorder, downregulation of BDNF mRNA expression in the hippocampus is believed to be an important pathogenesis. In a bipolar patient, lower BDNF levels in the blood and brain are observed during depressive and manic episodes than in the euthymic period[22-28].

Autism

Autism is a developmental disorder characterized by difficulties with social interaction and communication[29-32]. The patient with autism might express restricted and repetitive behaviour[29-32] BDNF is observed in autism. The regional downregulation at hippocampus is observed[29-32]. The role of BDNF in pathogenesis of autism is widely studied. All conditions associated with the autism spectrum disorder (ASD) show similar trends regarding BDNF concentration. The serum BDNF level is different in atypical autistic subjects (clinically milder phenotype) and typical ASD cases (clinically severe phenotype). Regarding the differential trend, lower DNF is observed in cases with more severe neuro-behavioural deficit[33].

Conclusion

The BDNF test is useful in diagnosis and follow-up of the patient. The determination of abnormal BDNF mRNA and protein expression can help identify the regional decreases or increases that are

pathognomonic findings in each disease. The peripheral BDNF test is also a new laboratory diagnostic test that helps monitor the progression of disease and response to therapy since the changed expression level in disorder is generally related to disease progression in the course of disease. In laboratory medicine, there are many important considerations regarding brain derived neurotrophic factors. The quality control in all phases, pre-analytical, analytical and post-analytical phases, for BDNF is necessary. Continuous developments in laboratory medicine lead to new advances in laboratory diagnosis for BDNF. The new diagnostic technologies such as applied Nano-Diagnostics for the BDNF diagnostic test are the future trend. The practitioner should recognize and update the data on laboratory diagnostic issues regarding BDNF.

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