



## SCIENTIFIC ARTICLE

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**Neuroscience and the New Scientific View of Leukemia****Hamida Ouled Slimane<sup>1\*</sup> and Raffaele Zinno<sup>2</sup>**

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**ABSTRACT**

Leukemia is a type of blood cancer in which blood stem cells develop abnormally and excessively in the bone marrow. Leukemia causes symptoms when abnormal white blood cells begin to replace healthy blood cells and spread. In addition to physical symptoms, such as pain, fatigue and shortness of breath, people with leukemia may also experience psychological symptoms such as depression or anxiety, as the disease alters the functioning of neurotransmitters and the Locus Coeruleus Locus, a brain nucleus involved, when dysfunctional in neurodegenerative diseases, in the control of the limbic system (memory, attention, concentration, control of anxiety and depression). This nucleus is directly or indirectly involved in the production of major neurotransmitters when it undergoes changes due to trigeminal input, it can determine the onset of psychiatric disorders, in particular depressive disorders and anxiety, panic attacks, experienced not only by the patient but also by the surrounding family context. Transcranial Magnetic Stimulation (TMS), together with neurophysiology, myofunctional therapy, posturology, psychiatry and psychotherapy, is included among the interventions that promote the development of the subject's neurotransmitters.

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**Introduction**

Leukemia is a type of blood cancer in which blood stem cells abnormally and excessively develop in the bone marrow. This type of disease originates from myeloid or lymphoid cells. Acute leukemias are made up of immature cells, while chronic leukemias are made up of mature cells. Advances in treatment and healthcare have substantially increased cancer survival rates in recent decades. Acute lymphoblastic leukemia (ALL), the most common cancer among pediatric cancer survivors, has achieved 5-year survival rates of over 90%, making concerns about quality of life after treatment more pertinent [1].

**Neurotransmitter Alterations**

In order to reduce neurotransmitter alterations and neurological deficits, modifiable risk factors must first be considered. Recent studies have shown that breastfeeding reduces the risk of children developing acute lymphoblastic leukemia in the future. The idea that breastfeeding may offer protection against childhood acute lymphoblastic leukemia is supported by biological credibility, given the fundamental role of breastfeeding in the formation of the intestinal microbiome and the immune system of the newborn. Aberrant immune responses to infectious stimuli play a central role in the development of B-cell precursor (BCP) acute lymphoblastic leukemia, the most common subtype of acute

lymphoblastic leukemia, in childhood. The suggested protective effect of breastfeeding against childhood cancer not only indicates potential biological pathways that could modulate the risk of childhood cancer, but also suggests a simple preventive measure, associated with a healthy diet, which excludes as much as possible overly processed or sugary foods. The recommendation shared by international experts is to follow a balanced, varied, healthy and moderate diet, therefore not excessively rich in red meat and carbohydrates. Consumption of olive oil is highly recommended, as it is rich in omega 3 and promotes the reduction of tumor plaques [2].

It is important to remember that stress and anxiety are also experienced by the family. The high intensity of the therapy, the long duration of the treatment and the unsatisfactory clinical outcomes not only affect pediatric patients but also represent a burden for those who take care of them, especially parents [3]. Neurocognitive areas affected include processing speed, attention, memory, executive function (e.g., working memory, cognitive flexibility), and academic performance [4]. Leukemia, therefore, causes neurotransmitter slowing and neurological morbidity due to central nervous system infiltration or vascular, metabolic, infectious, paraneoplastic, and treatment-related complications. Long-term neurocognitive decline can involve a variety of cognitive domains, which greatly affects the life-quality of patients with leukemia [5].

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Disturbance of the trigeminal system also causes stress, anxiety, and depression in the patient. Social skills may also be limited. It is unclear whether these effects are caused by treatment, cancer burden, or both. Understanding the late effects of treatment as well as the contribution of family functioning and coping behaviors to children's emotional functioning is vital in order to improve the quality of life of survivors. Current literature provides evidence that sensorimotor trigeminal activity associated with chewing can influence arousal, attention, and cognitive performance. These effects may be due to widespread connections of the trigeminal system to the ascending reticular activating system (ARAS), to which noradrenergic neurons of the locus coeruleus (LC) belong. LC neurons contain projections to the entire brain and their discharge is known to vary with pupil size. Therefore, if the effects of chewing on cognitive performance are mediated by the LC, it is reasonable to expect that changes in cognitive performance would be related to changes in task-related mydriasis. In other words, it could be said that trigeminal stimulation due to chewing activates the functioning of the mitochondria and, consequently, the neurophysiological system of the LC. In this way, neurotransmitters are activated, with particular attention to noradrenaline and all cognitive functions, thanks to the stimulation of some muscles of the stomatognathic system. The LC is the engine of this neurophysiological process, it stimulates and produces neurotransmitters, such as serotonin because the amino-acid-de-carboxylate, when not being activated by Noradrenaline, can increase the synthesis of serotonin, essential to avoid falling into depressive pathologies and to replace, in clinical cases that allow it, the use of antidepressant drugs that activate its production [6].

These data are particularly significant if we consider that several scientific publications have reported that parents of pediatric patients with leukemia suffer from comparative risks of psychological disorders, such as anxiety, depression and post-traumatic stress disorder (PTSD), which can be induced by the physical pain of their children, the economic strain of treatments, the challenge of social isolation, worries about their own health, the responsibilities of providing supportive care, etc [7]. From this perspective, it becomes clear why the disease must be considered as an estrogenic element against to be fought not only by the patient, but also by their family and clinical professionals, who, in various capacities, collaborate to improve the quality of life from a medical, psychological and social perspective. As highlighted by Kunin-Batson et al, a significant percentage of children experience emotional distress during and after leukemia therapy [8]. These data provide a compelling motive for a targeted early screening and psychosocial interventions to support family functioning and coping skills. Understanding risk factors for children's emotional-behavioral functioning after leukemia treatment is important to better identify those at greatest risk for future difficulties and to clarify possible paths of intervention. The months immediately following

the completion of treatment are described as one of the most difficult and anxiety-provoking periods for cancer patients and their families, presumably due to fear of relapse and loss of clinical support. The possibility of persistent neurobehavioral side effects from corticosteroids, as well as post- traumatic stress,

may also influence survivors' emotional-behavioral functioning after treatment [8].

### Multidisciplinary Approach

A multidisciplinary approach therefore becomes fundamental, taking in account even the “invisible” aspects of the disease. The analysis of depression disorders is already analyzed through the use of the pupillometer which, by recording the size of the pupil, verifies the activity of the LC and its modification due to the trigeminal input. **The Locus Coeruleus is a brain nucleus involved, when dysfunctional in neurodegenerative diseases, in the control of the limbic system (memory, attention, concentration, control of anxiety and depression). This nucleus is directly or indirectly responsible for the production of the major neurotransmitters. Acetylcholine and Noradrenaline are produced locally, Serotonin and Melatonin by the pineal gland following cerulean stimulation, Dopamine originates from the Substantia Nigra, also following cerulean stimulation.** Observing how the pupil reacts to light, therefore, could help predict recovery from depression and personalize the treatment of major depressive disorder through transcranial magnetic stimulation (TMS). This is a safe and non-invasive technique that uses magnetic fields to stimulate the parts of the brain involved in mood regulation. Therefore, Transcranial Magnetic Stimulation (TMS), together with neurophysiology, myofunctional therapy, posturology, psychiatry and psychotherapy, is included among the interventions that promote the development of the subject's neurotransmitters [9]. It is also possible to intervene with pediatric patients through a playful approach, suitable for the specific developmental age, such as drama therapy. and therapeutic puppetry, which reduce fear and anxiety related to diagnostic or therapeutic procedures in pediatric cancer patients. An important motivational factor for children is represented by compliments for their good behavior and for successful cooperation during the diagnostic or therapeutic procedure. This suggests that the inclusion of psychological preparation through a puppet game becomes fundamental in therapeutic nursing care to reduce anxiety and stress in the patient. The use of play therapy is particularly effective in children as a form of prevention and treatment and is mainly suitable for preschool and school-age children. It is a useful tool to address various emotional and behavioral problems, it can provide an approach to improve psychosocial outcomes for children with leukemia and to improve well-being during hospital stay [10].

As for parents, instead, among the most effective psychological interventions we can mention narrative writing and conversations elicited by emotions [11,12]. Narrative writing of emotional and distressing experiences promotes self-reflection and emotional regulation and reduces emotional sensitivity and inhibition, improving mental problems in parents of children undergoing stem cell transplantation [13,14].

### Conclusions

In light of the data considered so far, future research hopes to explore the usefulness of screening for psychological distress and the effectiveness of multidisciplinary interventions based

on the reactivation of neurotransmitters, lifestyle, rehabilitation and reduction of symptoms of anxiety, stress and depression, in the prevention and treatment of psychological distress in the patient and their family.

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