https://doi.org/10.31925/farmacia.2021.3.19 **ORIGINAL ARTICLE**

THE ROLE OF SERUM IONS DEFICIENCIES IN THE PATHOGENIC MECHANISMS OF ONCOLOGICAL DEPRESSION: PSYCHO-PHARMACOLOGICAL PARTICULARITIES

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Abstract

Cancer patients frequently present symptoms of depression and anxiety that influence the quality of life, compliance and adherence to treatment, disease progression and the overall survival. Psychiatric pathology could be related to the disturbance of serum ion levels, caused by the oncological or psychiatric status and the adverse effects of pharmacological treatment. This article is focused on assessing the relationship between anxiety, depression and stress and serum ion levels. Changes in the homeostasis of serum ions and pH may be factors that favour the risk of oncogenesis in the context of this psychiatric pathology. Knowledge of the involvement of serum ions in specific pathogenic mechanisms suggests the importance of monitoring them in oncological pathology with depression and helps to develop personalized psychopharmacological strategies.

Rezumat

Pacienții cu cancer prezintă frecvent simptome de depresie și anxietate care influențează calitatea vieții, complianța și aderența la tratament, evoluția bolii și supraviețuirea generală. Patologia psihiatrică ar putea fi legată de perturbarea nivelurilor serice ale ionilor, cauzată de statusul oncologic sau psihiatric și de efectele adverse ale tratamentului farmacologic. Prezentul articol este axat pe evaluarea relației dintre gradele de anxietate, depresie și stres și nivelul ionilor serici. Modificările homeostaziei ionilor serici și ale pH-ului pot fi factori care favorizează riscul de oncogeneză în contextul acestei patologii psihiatrice. Cunoașterea implicării ionilor serici în mecanisme patogenice specifice sugerează importanța monitorizării acestora în patologia oncologică cu depresie și ajută la elaborarea unor strategii psihofarmacologice personalizate.

Keywords: depression, anxiety, serum ions, cancer

Introduction

Psychiatric comorbidities such as depression and anxiety affect a large percentage of oncology patients, the prevalence being higher than in the general population (20% *vs*. 5% for depression, 10% *vs*. 7% for anxiety) [50]. Such comorbidities are often associated with a poor prognostic, by influencing adherence to treatment, the quality of life and the overall survival [43, 45, 69]. Even though they have a great impact on the survival of the patient, because they are considered a normal response to a traumatic life-changing experience such as cancer diagnosis [66], they are often disregarded during treatment. Depression and anxiety could manifest with fatigue, poor concentration, insomnia or hypersomnia, loss of appetite and weight, nausea, headache and abdominal or muscle pain [3, 58].

Often, these symptoms are considered a side effect of the treatment or oncological disease, which is why psychiatric examination is not recommended. Depression-like symptoms could also be influenced by cancer medication, such as immunotherapy (interferon-α is reducing the dopaminergic transmission in the brain) and chemotherapy (loss of appetite, nausea, fatigue). [38, 49, 55] Chemotherapy may also cause a decrease in serum ion levels, and these electrolytes disorders may be linked to depression, anxiety and stress [6, 33, 47].

Oncological pathology is a major public health priority, due to the increased incidence, significant management challenges and last, but not least due to economic considerations. Great importance is given to costly specific biomarkers by therapeutic protocols, which help to objectively assess the positive diagnosis potential. There isn't enough data regarding the negative evolution anticipation based on biological markers. Most cancer patients have a depressive disorder, either as a primary pathology prior to cancer diagnosis or as a secondary pathology to cancer diagnosis.

The depressive disorder has important biological markers (proinflammatory, cytokine and endothelial markers). Studies regarding oncological depression demonstrated a correlation of the negative evolution of neoplastic disease, when antidepressant therapies reduced psychiatric symptoms (depression, anxiety), but an ascending trend in biological markers for depression persisted.

The present study debates the significance of monitoring ionic indicators in oncology, specifically sodium, calcium, iron, potassium, magnesium and chloride, which can be easily evaluated at a low cost. These results are independent to the psychometric assessment used in psycho-oncology, primarily focused on stress and emotional disorders evaluation. Usually, the oncology physician minimizes the significance of these assessments, contrary to their high potential to predict the unfavourable evolution.

The negative prognostic is determined by the magnesium and sodium ions present in multiple enzymatic and molecular biochemical chains that favour the carcinogenetic process. Magnesium and sodium deficiency can cause neuropsychiatric disorders, which may indicate the worsening of the oncological disease, these being, in fact, the psychiatric manifestations of ionic imbalances. In our opinion, recognizing the importance of monitoring these markers, would also determine changes in therapeutic strategies, because there are no oncological therapies changes required, but only an adequate hydro-electrolytic rebalancing.

Materials and Methods

Study design. The design of the study was cross-sectional. The study population included oncology patients treated in the Oncology Department of the CF2 Clinical Hospital. The study was approved by the Ethics Committee of the hospital and all subjects were provided an inform consent regarding the participation in the study.

Inclusion criteria were age over 18, histopathology diagnosis of cancer, at least one line of treatment, no diagnose of psychiatric comorbidity or psychiatric treatment, the ability to understand and give consent regarding the participation in the study. 152 patients were included in the study with all types of cancer and in all stages.

Blood samples were collected and were analysed using Ventana method for serum ionogram, including iron, calcium, sodium, potassium, chloride and magnesium ions. Besides the testing of biological markers, the subjects were given the DASS 21R questionnaire for depression, anxiety and stress assessment [48, 53].

Statistical analysis. Statistical analysis was performed with SPSS 22 soft-ware for Windows PC. Qualitative data was represented as number and percentage. The indicators minimum, maximum, average and standard deviation were used for quantitative, continuous variables. The one-way Anova test was used to analyse the difference between the averages of the quantitative variables (iron, calcium, sodium, potassium, chloride and magnesium) by the degree of mental distress (depression, anxiety and stress). The level analysis was performed with the Bonferroni post hoc test for paired groups. The Spearman correlation analysis was used to determine the relation-ship between ion levels and levels of depression, anxiety and stress. The statistical significance of the analysed parameters was established at $p < 0.05$.

Results and Discussion

According to the demographic analysis of the patients included in the study, 77.65% are over the age of 61, females predominate (69.1%) and the most common cancer locations are ovarian, lung, colon and breast. The severe and extremely severe degree for depression, anxiety and stress occurs in 32.2%, 55.35% and 30.3% of the cases (Table I).

Table I

Demographic and clinical characteristic of the study population (N = 152)

Variables	Characteristics	Number / percentage (%)
Age (years)	≤ 50	7 / 4.6
	51 - 60	27 / 17.8
	61 - 70	41 / 27
	≥ 71	77 / 50.6

Sex	Female	105 / 69.1
	Male	47 / 30.9
Variables	**Characteristics**	**Number / percentage (%)**
Tumour location	Colon	24 / 15.8
	Gastric	12 / 7.9
	Ovary	59 / 38.8
	Lung	29 / 19.1
	Breast	23 / 15.1
	Thyroid	5 / 3.3
Residence	Rural	55 / 36.2
	Urban	97 / 63.8
Depression	Normal	56 / 36.8
	Mild	4 / 2.6
	Moderate	43 / 28.4
	Severe	24 / 15.8
	Extremely severe	25 / 16.4
Anxiety	Normal	28 / 18.4
	Mild	25 / 16.4
	Moderate	15 / 9.9
	Severe	14 / 9.2
	Extremely severe	70 / 46.1
Stress	Normal	68 / 44.7
	Mild	22 / 14.5
	Moderate	16 / 10.5
	Severe	19 / 12.5
	Extremely severe	27 / 17.8

Table II

Serum ion levels analysis

Serum ion	Normal range	Unit	Minimum	Maximum	Mean	Std. deviation
Iron	60 - 180	mcg/dL	18.00	146.00	± 65.90	± 8.643
Calcium	8.80 - 10.60	mg/dL	6.80	11.50	± 8.74	± 1.077
Sodium	135.00 - 148.00	mmol/L	127.00	144.00	± 132.28	± 5.13
Potassium	3.50 - 5.30	mmol/L	3.00	5.70	± 4.56	± 0.57
Chloride	98.00 - 107.00	mmol/L	95.00	106.51	± 101.76	± 3.85
Magnesium	1.90 - 2.50	mg/dL	1.46	2.21	± 1.76	± 0.27

mcg/dL = micrograms *per* decilitre; mg/dL = milligrams *per* decilitre; mmol/L = millimoles *per* litre

Serum ion analysis reveals that all six ions tested have values that are lower than the minimum normal values. The mean value for calcium, sodium, and magnesium is also low (Table II).

Low levels of iron ($r = -0.687$, $r = -0.679$, $r = -0.557$, $p < 0.001$) and sodium ($r = -0.642$, $r = -0.664$, $r = -0.575$, $p < 0.001$) have highly negative correlations with the degree of depression, anxiety and stress. The decrease in serum calcium had a moderate correlation degree with depression, anxiety and stress ($r = -0.357$, $r = -0.358$, $r = -0.234$, $p < 0.001$ and $p = 0.004$), whereas the correlation with chloride was small for depression ($r = -0.225$, $p = 0.005$) and anxiety ($r = -0.221$, $p = 0.006$).

Gender analysis reveals that depression, anxiety and stress have highly negative correlations with iron and sodium levels in women. Also, there is medium correlation for calcium and low correlation for chloride. For men, the levels of depression, anxiety and stress are found to be very high negatively correlated for iron and sodium and medium for chloride. A low level of these ions leads to an increased level of depression, anxiety and stress (Table III).

High negative correlations were found in gastric cancer, for sodium, in depression and anxiety, in the ovary for iron in depression and anxiety, in the lung for sodium in depression, iron and potassium in anxiety. The following cancer localizations had high negative correlations: colon for iron in depression and anxiety, gastric for sodium in stress, ovary for sodium in depression, anxiety, and stress, calcium in anxiety and iron in stress, lung for sodium in anxiety and stress and iron in depression, breast for calcium in anxiety and sodium in anxiety and stress. Negative correlations have a medium level in: colon cancer for iron in stress and sodium in anxiety, ovary for calcium and chloride in depression and stress, lung for potassium in depression, breast for iron in depression, anxiety and stress and calcium in depression and stress.

The average magnesium level according to the degree of depression, anxiety, and stress shows a low level for moderate-severe forms, but with no statistically significant differences. Using the Anova test and

the Bonferroni post hoc analysis, it was noticed that magnesium levels in women with severe or extremely severe depression are statistically significantly lower than in women with mild depression, with an average value of 0.51 (CI: -0.91 — 0.124, p = 0.003), respectively 0.44 (CI: -0.83 — 0.05, p = 0.016). There were no statistically significant differences in anxiety and stress for males.

Table III

Correlations between serum ion levels and depression, anxiety and stress, for all subjects, males and females

Correlations Spearman's rho			Depression	Anxiety	Stress
Total lot N = 152	Iron	r	-0.687	-0.679	-0.557
		p	< 0.001	< 0.001	< 0.001
	Calcium	r	-0.357	-0.358	-0.234
		p	< 0.001	< 0.001	0.004
	Sodium	r	-0.642	-0.664	-0.575
		p	< 0.001	< 0.001	< 0.001
	Potassium	r	0.123	0.104	0.009
		p	0.131	0.203	0.908
	Chloride	r	-0.225	-0.221	-0.152
		p	0.005	0.006	0.062
	Magnesium	r	-0.065	-0.124	-0.030
		p	0.428	0.127	0.714
Female gender N = 105	Iron	r	-0.642	-0.598	-0.516
		p	< 0.001	< 0.001	< 0.001
	Calcium	r	-0.422	-0.388	-0.272
		p	< 0.001	< 0.001	0.005
	Sodium	r	-0.555	-0.583	-0.495
		p	< 0.001	< 0.001	< 0.001
	Potassium	r	0.141	0.090	0.028
		p	0.152	0.361	0.780
	Chloride	r	-0.232	-0.209	-0.165
		p	0.017	0.033	0.092
	Magnesium	r	-0.019	-0.080	-0.021
		p	0.850	0.419	0.834
Male gender N = 47	Iron	r	-0.742	-0.790	-0.612
		p	< 0.001	< 0.001	< 0.001
	Calcium	r	-0.125	-0.180	-0.080
		p	0.402	0.226	0.594
	Sodium	r	-0.835	-0.816	-0.747
		p	< 0.001	< 0.001	< 0.001
	Potassium	r	-0.021	0.067	-0.107
		p	0.887	0.656	0.472
	Chloride	r	-0.287	-0.343	-0.174
		p	0.050	0.018	0.241
	Magnesium	r	-0.100	-0.192	-0.021
		p	0.504	0.197	0.889

Table IV

Correlations between serum ions and cancer localization and depression, anxiety and stress levels

Correlations Spearman's rho			Depression	Anxiety	Stress
Colon cancer N = 24	Iron	r	-0.664	-0.527	-0.418
		p	< 0.001	0.008	0.042
	Calcium	r	-0.326	-0.034	-0.052
		p	0.120	0.873	0.810
	Sodium	r	-0.252	-0.423	-0.284
		p	0.235	0.040	0.178
	Potassium	r	0.148	0.179	0.180
		p	0.491	0.402	0.400
	Chloride	r	-0.002	-0.306	-0.047
		p	0.994	0.145	0.826
	Magnesium	r	0.220	-0.142	0.177
		p	0.301	0.508	0.408

Correlations Spearman's rho			Depression	Anxiety	Stress
Gastric cancer N = 12	Iron	r	-0.571	-0.404	-0.400
		p	0.053	0.193	0.198
	Calcium	r	-0.520	-0.249	-0.443
		p	0.083	0.435	0.149
	Sodium	r	-0.860	-0.863	-0.627
		p	< 0.001	< 0.001	0.029
	Potassium	r	-0.178	-0.125	0.068
		p	0.580	0.700	0.833
	Chloride	r	-0.348	-0.565	-0.013
		p	0.268	0.056	0.968
	Magnesium	r	-0.453	-0.529	-0.196
		p	0.139	0.077	0.541
Ovarian cancer N = 59	Iron	r	-0.725	-0.718	-0.662
		p	< 0.001	< 0.001	< 0.001
	Calcium	r	-0.424	-0.527	-0.340
		p	0.001	< 0.001	0.008
	Sodium	r	-0.636	-0.587	-0.566
		p	< 0.001	< 0.001	< 0.001
	Potassium	r	-0.009	-0.082	-0.069
		p	0.946	0.536	0.606
	Chloride	r	-0.344	-0.230	-0.301
		p	0.008	0.079	0.020
	Magnesium	r	-0.105	-0.240	-0.116
		p	0.427	0.067	0.382
Lung cancer N = 29	Iron	r	-0.611	-0.918	-0.335
		p	< 0.001	< 0.001	0.075
	Calcium	r	-0.123	0.090	0.137
		p	0.524	0.644	0.479
	Sodium	r	-0.793	-0.635	-0.567
		p	< 0.001	< 0.001	0.001
	Potassium	r	0.458	0.869	0.226
		p	0.012	< 0.001	0.238
	Chloride	r	-0.034	-0.027	-0.010
		p	0.862	0.888	0.960
	Magnesium	r	-0.110	0.308	-0.100
		p	0.568	0.104	0.605
Breast cancer N = 23	Iron	r	-0.474	-0.458	-0.550
		p	0.022	0.028	0.007
	Calcium	r	-0.478	-0.681	-0.456
		p	0.021	< 0.001	0.029
	Sodium	r	-0.328	-0.593	-0.621
		p	0.126	0.003	0.002
	Potassium	r	0.093	-0.104	-0.330
		p	0.674	0.636	0.124
	Chloride	r	-0.133	0.032	-0.066
		p	0.545	0.885	0.765
	Magnesium	r	0.200	0.128	0.311
		p	0.359	0.561	0.149

Hyponatremia is frequently associated with orthostatic hypotension and minor traumatic brain injury (mTBI) following falls. In mTBI, hyponatremia may occur, which, untreated, aggravates the progression of brain injuries and favours the establishment of post-traumatic depression [38]. This can exacerbate the rapid cognitive deficit that develops in a patient with neoplastic disease and depressive-anxiety disorder. The aggressiveness of amyloid beta (Aβ) neurodegenerative elements increases in the elderly, suggesting Alzheimer's disease. The accentuation of neurodegenerative processes after mTBI is determined by the dysfunction of the glymphatic pathway [20]. In these patients, selective serotonin reuptake inhibitor (SSRI) class antidepressants therapy promotes the development of severe hyponatremia, creating a vicious circle of unfavourable patient evolution. The central pathogenic mechanism is represented by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The characteristic clinical aspect is defined by the contrast between the

low level of serum sodium and the absence of oedema. In this context, antidiuretic therapy, tumour processes, hypothyroidism, or respiratory or cerebral diseases amplify SIADH, worsening the prognosis of the neoplastic disease [28].

In cancer, the emergence of somatic and psychiatric comorbidities, especially chronic pain, requires the association of drugs that can increase serum sodium deficiency (antidiuretics, antidepressants, antiepileptics used to treat seizures caused by brain metastases or for analgesic effects – gabapentin, pregabalin), independent of oncological medication [21, 36, 61]. Treatment with SSRI antidepressant can also cause hyponatremia [23], which alters the normal function of natriuretic peptides (NPs), causing SIADH. As a consequence, they should be avoided in cases of oncological depression and strict monitoring of serum sodium levels is required. Hyponatremia, which is associated with low levels of natriuretic peptides, can be used to predict a major cardiovascular risk (myocardial infarction) [5]. The administration of antipsychotic medication has a cardiotoxic risk in patients with moderate-severe oncological depression or specific terminal-phase psychomotor agitation, especially in those with elevated N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) levels [19, 64]. This risk is amplified by using antipsychotics that prolong the QT interval [27], which is why this medication is contraindicated [12].

The pathogenic significance of hyponatremia is also linked to the disruption of sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) activity, an enzyme that can cause ischemia, depression, memory and learning disorders and cognitive impairment in the brain [8, 14]. This is an indirect mechanism of action of hyponatremia on neural function, with the direct mechanism being the impairment of sodium channel and pump functionality due to ionic deficiency.

Pathogenic mechanisms dominated by hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and high levels of endogenous cortisol cause a decrease in neurogenesis in the hippocampus, resulting in intra-hippocampal dysconnectivity and atrophy, exacerbating the cognitive deficit. In the conditions of oncological depression, the cognitive deficit determines the decrease of the patient's adherence and compliance with the treatment for oncological, antidepressant and non-pharmacological treatment. Noncompliance or therapeutically uncontrolled depression activates the cellular mechanisms of depression (inflammation, endothelial dysfunction and cytokines storm), increasing the risk of neoplastic process progression or metastases (Figure 1).

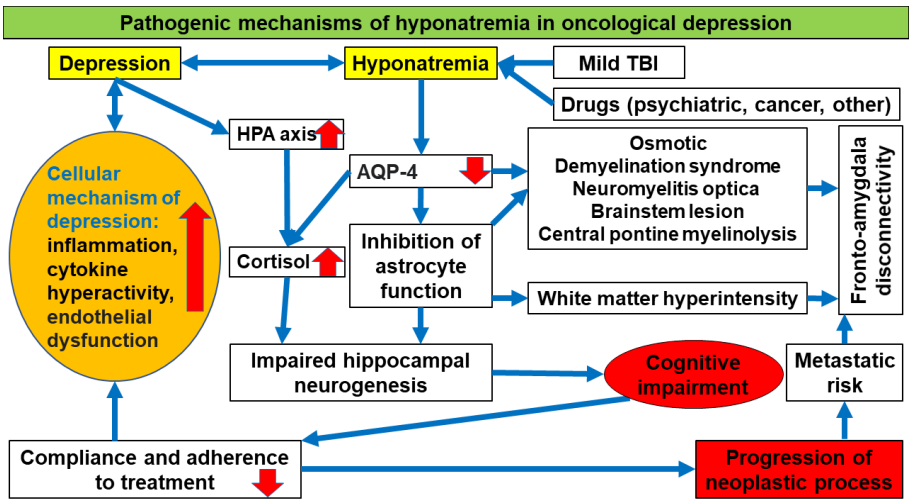

Figure 1.
Pathogenic mechanisms of hyponatremia in oncological depression

The fronto-amygdala disconnection syndrome is favoured by the demyelination syndrome associated with brain metastatic invasion, with the appearance of cognitive decline, adynamia, apathy, anhedonia, alternating with impulsive epileptoid disinhibition with self or hetero-aggressive behaviour [42]. This syndrome is suggested by the presence of white matter hyperintensities on cerebral neuroimaging examination. The presence of recent mTBI-associated hyponatremia predicts blood-brain barrier (BBB) disruption following decreased AQP4. Indirectly, this mechanism can induce brain metastasis by increasing BBB permeability [20, 26].

During current epidemiological conditions, the stress of patients with oncological diseases is greatly amplified and the persistence and intensity of stress favours the amplification of serum magnesium deficiency, which can act as an important pro-carcinogenic factor [10, 47]. The presence of hypomagnesemia is common in patients with chronic psychiatric disorders, who in the current pandemic status represents a real population at risk for the development of severe forms of COVID-

19, especially since there is a risk of adverse reactions to psychotropic medication, correlated with pro-inflammatory status, activation of cytokine factors, oxidative stress and cardiometabolic syndrome [35].

Disruption of Na^+/K^+-ATPase activity causes a functional imbalance between the receptors of the cerebral glutamatergic system, respectively blocks α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in favour of hypo-reactivity of N-methyl-D-aspartate (NMDA) receptors, hyperactivity associated with cerebral apoptotic mechanisms [4]. The pathogenic mechanisms of hypomagnesemia in depression are dominated by endogenous hyper-cortisolemia and increased excitotoxic activity of glutamate. The relationship between depression and hypomagnesemia is bidirectional by exacerbating each other [1, 57]. Low magnesium level increases the action of glutamate and decreases brain-derived neurotrophic factor (BDNF) [63]. In general, there is little consideration of the fact that hypomagnesemia is associated with amplification of HPA axis hyperactivity and potentiates thrombotic phenomena. Thrombotic microangiopathy can be anticipated by identifying decreased von Willebrand factor (VWF) and platelet activity. It is known that oncological diseases associate thrombotic risks [32]. On the other hand, in some situations the occurrence of thrombosis can be a paraneoplastic sign that anticipates the genesis of a malignant tumour. The decrease in VWF associated with the increase of hypoxia-inducible factors (HIFs) suggests, in the conditions of thrombotic angiopathy, the increase of the activity of proangiogenic and tumorigenic factors, with risk of oncological evolution [15]. Medium or severe TBI causes hypomagnesemia, which causes unfavourable evolution and significant cognitive sequelae [45]. Identification and correction of low magnesium level increases neuroprotection and promotes the functional recovery of cognitive structures and circuits (Figure 2).

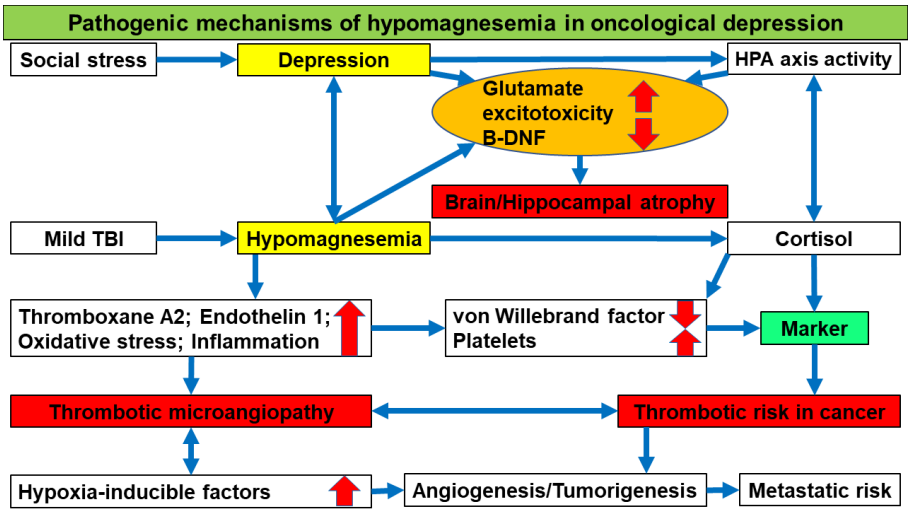

Figure 2.
Pathogenic mechanisms of hypomagnesemia in oncological depression

Hypocalcaemia in depressive disorder may be correlated with changes in parathyroid function or with a primary hypoparathyroidism. Common associations between hypocalcaemia and hypomagnesemia have been identified in bipolar depression [55]. Hypocalcaemia is associated with the risk of inducing epileptiform manifestations, which in the case of oncological depression can cause problems with differential diagnosis, especially in the presence of cerebral metastases. At the same time, hypocalcaemia is involved in magnesium depletion, the mechanisms of hypomagnesaemia being increased by decreased serum calcium [17, 18, 58].

Fundamental research has shown that calcium deficiency increases the level of free plasma fatty acids, inducing acute pancreatitis. This condition, especially in recurrent types, is associated with the risk of developing pancreatic cancer. Acute pancreatitis associated with hypocalcaemia has a major risk for pancreatic cancer. In patients with pancreatic cancer and depression, hypocalcaemia is an important indicator of adverse outcome [16]. The history of multiple episodes of acute pancreatitis significantly decreases the survival rate of pancreatic cancer patients. The presence of hypocalcaemia may indicate a neuroendocrine disorder dominated by imbalances induced by hypoparathyroidism, and this type of pancreatic cancer requires complex investigation and multidisciplinary monitoring.

The connection between depression, hypocalcaemia and cancer is amplified by the presence of high levels of endogenous cortisol, following anxiety and chronic stress triggered by oncological diagnosis. Hypercortisolaemia favours hypocalcaemia, but also the risk of osteoporosis and spontaneous fractures, which complicates the patient's clinical picture. Hypocalcaemia and hypercortisolaemia promote thrombosis and the

risk of embolic events that can sometimes endanger the patient's life. This mechanism is suggested by the presence of high thrombotic risk, similar to the pathogenic pattern of Cushing's disease [13, 65]. The main markers of thrombotic risk are decreased VWF and increased C-reactive protein (CRP), interleukin (IL) 6, IL-8. In adenocarcinomas and pancreatic neuroendocrine tumour, monitoring IL-8 levels becomes equally important as histopathological and immunohistochemical evaluations [41, 62].

In certain brain conditions, either tumour type [37], either of the infectious type [11, 29], the clinical picture may be dominated by depression, which generally masks the symptoms of the underlying disease. Therapeutic resistance to depression may be an alarm indicator that requires a reassessment of the diagnosis. Resistant depression is correlated with the imbalance in the efficiency of dopaminergic transmission between the basal ganglia and the frontal cortex, and therapeutic interventions with SSRI antidepressants or antipsychotics can aggravate depression.

This type of depression is caused by frontal dopaminergic deficiency by functional alteration of D1 receptors [9, 60] and blocking of D2 receptors in the basal ganglion area, favouring the disconnection of dopaminergic transmission between the two brain structures [40]. The use of dopamine agonists is being investigated pharmacologically for their potential antitumor effect. Dopamine deficiency can be considered a marker of tumorigenic risk, and the possibility of investigating the L-dopa agonist [53, 68] offers a possibility to evaluate the functional status and pathogenic roles of the dopaminergic system. On the other hand, oncological depression, due to high cortisol levels, determines a major risk of diabetes, especially in the administration of antidepressant and antitumor drugs, which induce disorders of carbohydrate metabolism [2]. Depression is also correlated with latent hypocalcaemia. Convulsive manifestations following a low level of calcium, suggest in depression the mood shift to a hypomanic or manic episode. For this reason, mood stabilizing antiepileptic therapy is becoming a major indication in depressive disorder with hypocalcaemia.

Decreased serum chloride is associated with metabolic alkalosis which is a predictor of mortality [34], regardless of the location of the cancer. In the critical moments of the evolution of the oncological disease, the rebalancing of the acid-base level is an imperative requirement. The lack of adequate and timely therapeutic intervention causes an endogenous compensation of pH homeostasis, causing metabolic acidosis, with massive release of lactic acid that causes neuronal and glial apoptosis in the brain [31]. These neural changes are associated with rapid and intense cognitive impairment.

The decrease of serum chloride and the promotion of metabolic alkalosis can be induced by the excessive use of proton pump inhibitors, intensely used in the prevention of gastrointestinal adverse events induced by oncological medication. pH monitoring could become an important indicator of the adaptation of therapeutic strategies in oncological pathology associated with depression, anxiety and stress. In breast and prostate cancer, proton pump inhibitors can induce an increase in prolactin with tumour progression [22].

Low iron levels in patients with depression and anxiety in oncological context is difficult to integrate into a pathogenic model, because there are haematotoxic mechanisms induced by pharmacological oncological therapies, radiotherapy and surgery. The only observation we can consider valid is the association of depression with a high level of cortisol, which can promote gastrointestinal micro-haemorrhages, with risk of iron deficiency anaemia. Occult haemorrhages can be favoured by the association of concomitant medication (analgesics, NSAIDs, anticoagulants), with oncological therapy [24].

The pathogenic patterns presented can be confirmed or denied by further research. The clinical-biological condition of patients with oncological depression requires multiple therapeutic combinations, which can promote ionic imbalances. Due to the oncogenic risk, serum ions monitoring can bring benefits in both psycho-oncology and clinical psychiatry. This risk can also be determined by untreated depression or with incomplete remission, through specific cellular pathogenic mechanisms, which can be accentuated by ionic imbalances. Although not considered important, the association between depression and ionic imbalance can be an alarm indicator in oncological depression, which can be used in oncological prevention strategies.

Conclusions

Depression, anxiety and stress are important co-morbidities of the cancer patients and could determine a poorer quality of life and a lower life expectancy. Their symptoms could be misinterpreted as effects of the disease or the treatment, thus patients would not receive a proper treatment. Clinicians should take into consideration that biologic factors such as serum ions could influence the degree of depression and anxiety. All oncology patients should be screened for depression and anxiety symptoms, and, if the screening tests are positive, both blood tests and psychiatric consult should be performed, in order to offer a personalized treatment for these patients.

Conflict of interest

The authors declare no conflict of interest.

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