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The Relationship between Anxiety and Immunity in Pediatric Oncology Patients

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ABSTRACT

Background: Pediatric onco-hematology is not a frequently encountered medical specialty, and it influences everyday life, basic activities, and the immune system, mostly through psycho-social changes, which may affect every individual and their families differently. Anxiety is the most frequently encountered mental health disorder occurring during childhood and adolescence. The effect of stress and anxiety on the immune system is suggested by the fact that stress hormones elevate proinflammatory cytokines and subsequently lower the anti-inflammatory response. **Objective:** Our main objective was to analyze the relationship between anxiety disturbance and cytokine levels in oncologic pediatric patients from Târgu Mureș in order to answer the following question: does anxiety influence immunity? **Material and methods:** After testing pediatric oncology patients from the Pediatrics Clinic no. 2 of Târgu Mureș, Romania with the SCARED child test, we took blood samples from each participant. IL-6, IL-10, IL-1β, IL-12p40 and TNF-α levels were evaluated with a Human Cytokine Magnetic Panel using the xMAP technique on Flexmap 3D platform (Luminex Corporation, Austin, USA). C-reactive protein levels were determined with the BN Pro Spec nephelometer with CardioPhase hsCRP (Siemens Healthcare Diagnostics, GmbH, Marburg, Germany) reagent. **Results:** The 46 pediatric oncology patients had 6 main diagnostic groups, the most frequent pathology was acute leukemia (58.7%) followed by malignant solid tumors (21.74%) and lymphomas (6.52%). In the anxious group (45.65%) we observed 4 of the 5 studied anxiety types: panic disorder, separation, social, and generalized anxiety. We measured the cytokine levels of all the participants from the two main groups: anxious/non-anxious. Statistical analysis (linear regression) showed statistically significant positive correlations in the anxious group related to the IL-1β and IL-6, a moderate/weak correlation related to IL-12p40, as well as a negative moderate correlation between IL-10 values in the anxious group and a positive trend in the non-anxious group. **Conclusions:** Psycho-oncology is a relatively young specialty with few studies in the last two decades. IL-1β, IL-6, and TNF-α present high levels in anxious patients, while IL-10 and IL-12p40 have low serum levels in mental disorders. C-reactive protein levels are not influenced by anxiety.

Keywords: anxiety disorder, pediatric oncology, inflammatory cytokines, immune response

INTRODUCTION

Pediatric onco-hematology is not a frequently encountered medical specialty, and it presents a heavy psychological and social influence, as these disorders affect both the pediatric patients, as well as their family members, with profound consequences on everyday life and basic human functions, while also impacting the immune system.[1] Therapeutic options vary with each pathology group and consist of chemotherapy, surgical treatment, radiotherapy, and bone marrow transplant according to international protocols for each diagnosis.

Cytostatic courses are followed by temporary medullary aplasia with septic or bleeding complications. In case of acute leukemia, secondary bone marrow aplasia is much longer and more severe than in the case of solid tumors or lymphomas with shorter duration, which are much easier to correct.[2,3]

In pediatric oncology, the prolonged hospitalization period, uncertainty regarding the future, social isolation and seclusion from family members, oncological therapies (radio- and chemotherapies), as well as the presence of intracranial tumors or metastases can have a direct negative impact on the psychological wellbeing of the pediatric patients.[4,5] Furthermore, the harsh and prolonged treatments, as well as the imminent death threat may create traumatic sequelae in the child's psychic function and maturation process.[4]

Children with malignancies and their families must face a prolonged period of medical treatment in the hospital, with a tremendous uncertainty regarding their future. All members of these families can suffer from emotional distress on a short or long term.[5]

Anxiety is the most frequent mental disorder that occurs in children and adolescents, 15–20% of individuals experiencing anxiety at some point in their life. If ignored, the symptoms may prolong throughout adulthood and lead to psychosocial complications.[6] There are different types of anxiety disorders: separation anxiety, selective mutism, specific phobias, social anxiety, drug-induced anxiety, medical conditions-induced anxiety, panic disorder, agoraphobia, generalized anxiety, or school avoidance.[7]

Cytokines, as signaling molecules for the modulation of the immune response, can be present in the circulation in picomolar quantities. In cases of infection or inflammation, cytokine levels can rise to 1,000 times. Some cytokines have a proinflammatory role, others an anti-inflammatory role.[8]

The effect of psychological stress and anxiety on the immune system is triggered by the release of stress hormones, which lead to an overexpression of proinflammatory cytokines (IL-1, IL-6, TNF-α) and low levels of anti-inflammatory cytokines (IL-10, IL-12).[9,10]

Proinflammatory cytokines IL-1, IL-6, and TNF-α, and anti-inflammatory cytokines IL-4, IL-10, and IL-3 have a very important role in the pathogenesis of depression. Different immune responses have been observed according to the severity, nature, and duration of the stress factor: severe stress alters immunity through time, while moderate stress stimulates immune reactions, as shown by Glaser *et al.*[11] The same study demonstrated that the concentration of proinflammatory cytokines rises in the plasma of depressive patients and recedes after healing.[11]

OBJECTIVE

Our main objective was to find a correlation between anxiety disorder and cytokine levels in pediatric oncology patients from Târgu Mureș, Romania. Secondary objectives were to evaluate the frequency of anxiety in the oncologic pediatric population, to identify different anxiety types and compare them with anamnestic data in order to identify certain factors that influence anxiety. Another question that we would like to answer is: does anxiety influence immunity?

MATERIALS AND METHOD

Participants

After their parents completed the consent form, we tested pediatric oncology patients from the Pediatrics Clinic no. 2 of Târgu Mureș, Romania, aged between 7 and 21 years, diagnosed with malignant diseases until the age of 18 years.

Anxiety levels were analyzed using the SCARED child test, created in 1997 by Dr. Boris Birmaher, which can be used without a special license and comprises a personal questionnaire for anamnestic data. By completing the questionnaire, patients can be categorized in 5 types of anxiety disorders: panic disorder, generalized anxiety, separation anxiety, social phobias, and school avoidance.

Laboratory determination

We took blood samples from each participant. The samples were centrifuged, and the serum was stored at –80 °C.

IL-6, IL-10, IL-1β, IL-12p40, and TNF-α levels were measured with a Human Cytokine Magnetic Panel (EMD Millipore Corp, USA) using the xMAP technique. Serum samples were incubated with monoclonal antibody

TABLE 1. Summary of anamnestic data in the studied lot

		N	%
Age groups	7–10 years	16	34.8%
	11–13 years	15	32.6%
	14–16 years	7	15.2%
	17–21 years	8	17.4%
Gender distribution	Male	30	65.22%
	Female	16	34.78%
Provenance distribution	Urban	26	56.52 %
	Rural	20	43.48%
Education level	Primary	17	36.96%
	Middle	17	36.96 %
	Highschool	12	26.9%
Number of truancy months	0–3 months	18	39.13%
	4–6 months	14	30.43%
	7–9 months	4	8.7%
	10–12 months	7	15.22%
	>12 months	3	6.52%
Catheter presence	Yes	32	71.1%
	No	14	28.9%
Treatment phase	Chemotherapy	10	21.74%
	Remission	33	71.74%
	Does not correspond	3	6.54%
Anxiety	Yes	21	45.65%
	No	25	54.35%
Anxiety disorders	Separation	10	47.62%
	Generalized	2	9.52%
	Panic	2	9.52%
	Social	7	33.33%

marker spheres. Different reagent-adding steps were performed, followed by washing in order to obtain sandwich-like antigen-antibody complexes, which were analyzed on the Flexmap 3D platform (Luminex Corporation, Austin, USA).

CRP levels were determined with the BN Pro Spec nephelometer with CardioPhase hsCRP (Siemens Healthcare Diagnostics, GmbH, Marburg, Germany) reagent. The reference interval was <3 mg/L, with a measuring interval of 0.175–11 mg/L, minimal detection limit 0.175 mh/L, intra- and inter-run coefficient of variation <4.0% and <4.6%, respectively.

Statistical data analysis

Data has been centralized in a Microsoft Excel file and processed with the IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA) statistical program. Cytokine levels were evaluated with descriptive and interference statistics through the Wilcoxon test, and due to the fact that the data was widely spread, we eliminated extreme numerical values with the Grubbs (box-plot) test. The reviewed descriptive analysis enabled the use of the t test and linear regression method to highlight a correlation between anxiety and cytokine levels.

RESULTS

We tested 46 pediatric oncology patients aged between 7–21 years (mean 12.46 years, SD 3.361). Demographic and anamnestic data analysis is presented in Table 1.

Table 1. Summary of anamnestic data in the studied lot

The pathology was split into 6 main diagnostic groups, the most frequent pathology being acute leukemia (58.7%), followed by malignant solid tumors (21.74%) and lymphomas (6.52%).

The age group distribution related to pathology shows that leukemia and solid tumors are more frequent under the age of 13, and that lymphomas are more frequent in the 16–18 years age group.

Based on the SCARED test results we stratified the patients into anxious and non-anxious clusters (Table 1).

TABLE 2. Statistical results of the studied lots (anxious/non-anxious) according to the analyzed parameters

		Anxious		Non-anxious		p value
		N	%	N	%	
Age groups	≥7 ; ≤10	8	38.1%	8	32.0%	
	≥11; ≤13	10	47.6%	5	20.0%	
	≥14; ≤16	1	4.8%	6	24.0%	
	≥17; ≤21	2	9.5%	6	24.0%	0.074
Residence	Urban	11	42.3%	15	57.7%	
	Rural	10	50.0%	10	50.0%	0.604
Catheter	Yes	14	66.7%	19	76.0%	
	No	7	33.3%	6	24.0%	0.484
Diagnosis	Leukemia	10	47.6%	17	68.0%	
	Lymphoma	1	4.8%	2	8.0%	
	Malignant solid tumors	6	28.6%	4	16.0%	
	Border-line solid tumors	1	4.8%	1	4.0%	
	Benign solid tumors	3	14.3%	0	0.0%	
		0	0.0%	1	4.0%	0.283
Gender	Male	13	61.9%	17	68.0%	0.665
	Female	8	38.1%	8	32.0%	
Months of truancy	0–3 months	10	47.6%	8	32.0%	
	4–6 months	8	38.1%	6	24.0%	
	7–9 months	1	4.8%	3	12.0%	
	10–12 months	1	4.8%	6	24.0%	
	>12 months	1	4.8%	2	8.0%	0.277
Mothers' education level	0–4 grades	4	19.0%	0	0.0%	
	8 grades	6	28.6%	4	16.0%	
	High school	7	33.3%	9	36.0%	
	Postsecondary	0	0.0%	1	4.0%	
	University	4	19.0%	11	44.0%	0.060
Treatment	Yes	6	28.6%	4	16.0%	
	No	15	71.4%	21	84.0%	0.303
Siblings	No	4	19.0 %	5	20.0%	
	Yes (≤2)	16	76.2%	20	80.0%	
	Yes (>3)	1	4.8%	0	0.0%	0.719

In the anxious group we have observed 4 of the 5 studied anxiety types: panic disorder, separation, social, and generalized anxiety. None of our patients showed school-related anxiety. The incidence and frequency of different types of anxiety, as well as other anamnestic data are also shown in Table 1.

Most of the patients were admitted to the hospital with a first-degree relative (mother in 91.32% of cases and father in 2.22% of cases). Although there were no statistically significant differences between age groups in relation to the type anxiety disorder ($p = 0.537$), subjects aged under 13 years were more prone to present separation anxiety compared to other age demographics. Treatment complexity correlated with types of anxiety showed a statistically non-significant difference ($p = 0.061$). Correlations between the mother's level of education and the anxiety score show values close to the significant threshold ($p = 0.06$).

The anxiety-gender relationship was statistically non-significant ($p = 0.665$), as shown in Table 2.

Studying immunity in correlation with anxiety

We measured the cytokine levels of all the participants from the two main groups: anxious/non-anxious. The high standard deviation prompted us to identify the extreme values and to exclude them, as highlighted in Table 3.

Correlations between cytokine levels and the presence of anxiety are presented in Table 4.

Statistical analysis (linear regression) showed statistically significant positive correlations in the anxious group related to IL-1β and IL-6, a moderate/weak correlation

TABLE 3. The difference between mean IL serum levels in the studied lots

Anxious	N	Mean	SD	p value
Yes	9	1.82	2.50	0.016
No	34	1.35	1.27	
Yes	6	4.17	2.49	0.148
No	30	3.27	1.63	
Yes	10	12.45	9.61	0.645
No	31	9.61	14.29	
Yes	9	3.57	1.43	0.617
No	32	3.46	1.25	
Yes	9	30.21	12.97	0.680
No	34	25.72	12.77	
Yes	6	0.39	0.45	0.071
No	31	1.15	1.51	

in the anxious group related to IL-12p40, and a negative moderate correlation between IL-10 values in the anxious group and positive trend in the non-anxious group (Figures 1, 2, and 3).

DISCUSSIONS

Current literature data is scarce on the matter of the psycho-social impact of anxiety on pediatric oncology patients or their family members. However, the SCARED measuring tool has been developed for the quantification and categorization of anxiety and may be used without any special license or costs, its efficacy being comparable to other anxiety-measuring tools.

The 46 pediatric oncology patients included in our study had a mean age of 12.46 years (SD 3.361), with a preponderance of patients below the age of 13 years, similarly to other reports in the literature.[12] Male patients represented 65.22% of the study group, similarly to other studies which found that more than 60% of cases manifest in male patients.[13]

The pathology consisted in a variable number of diagnoses comprised in 6 large disease groups, the first and most frequent being acute leukemia in 27 cases (58.69%), followed by malignant solid tumors (bone tumors, renal tumors) in 10 cases (21.73%) and lymphomas in 3 cases (6.52%), similarly to data found in the specialty literature.[13]

Regarding the presence of a catheter, we have established that close to 2/3 of patients had a port system central venous catheter (CVC) or a tunneled central venous line. A CVC helps prevent the direct irritating effect of cytostatic treatments on the veins and provides a safe venous line.[14] We found no statistically significant correlation between the presence of a catheter and anxiety ($p = 0.484$).

In our study, 21 (45.65%) patients presented anxiety based on the SCARED test, this percentage being higher than the one described in the literature. We must mention that the number of studies on this subject is still low.[15] Of the 21 patients with anxiety, separation anxiety was present in 47.62% of cases (n = 10), followed by social anxiety in 33.33% of cases (n = 7). No patient has exhibited school anxiety. According to the data from the specialty literature, as far as chronic pathologies are concerned, the mother-child bond is stronger under the age of 13 years; furthermore, most patients in this age group have not been separated from their families for long periods of time, thus they have a decreased resistance to separation from the family environment.[15]

Separation anxiety is treated according to the age of the child at the time of initial diagnosis, and therapeutic measures often include decorating the hospital room with toys and personal objects from the patient's home. The type of anxiety is correlated with age, and our study found that separation anxiety was more frequent among patients aged

TABLE 4. The correlations between cytokine levels and the presence of anxiety

IL-1	Anxious	$r = 0.532$, $R^2 = 0.283$, $p = 0.019$	Statistically significant positive correlation in anxious patients, negative correlation in the non-anxious group
	Non-anxious	$r = -0.082$, $R^2 = 0.007$, $p = 0.352$	
IL-6	Anxious	$r = 0.742$, $R^2 = 0.551$, $p = 0.002$	Medium positive correlation in the anxious group and a medium negative correlation in the non-anxious group
	Non-anxious	$r = -0.308$, $R^2 = 0.095$, $p = 0.087$	
IL-10	Anxious	$r = 0.220$, $R^2 = 0.048$, $p = 0.365$	Negative correlation in the anxious group and a statistically insignificant positive trend in the non-anxious group
	Non-anxious	$r = 0.153$, $R^2 = 0.024$, $p = 0.248$	
IL-12p40	Anxious	$r = 0.006$, $R^2 = 0.000$, $p = 0.980$	Marked correlation in the anxious group and a weak negative correlation in the non-anxious group, both statistically insignificant
	Non-anxious	$r = -0.065$, $R^2 = 0.004$, $p = 0.385$	
TNF-α	Anxious	$r = 0.244$, $R^2 = 0.059$, $p = 0.314$	A very weak positive correlation in the anxious group and a descending trend in the non-anxious group
	Non-anxious	$r = 0.065$, $R^2 = 0.004$, $p = 0.382$	
CRP	Anxious	$r = 0.198$, $R^2 = 0.039$, $p = 0.445$	A weak positive trend in the anxious group and a slightly descending trend in the non-anxious group
	Non-anxious	$r = 0.192$, $R^2 = 0.037$, $p = 0.208$	

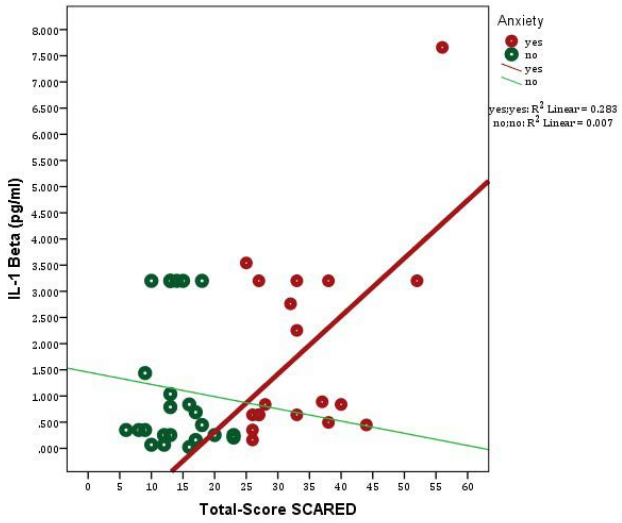

FIGURE 1. Linear regression between IL-1β and anxiety score

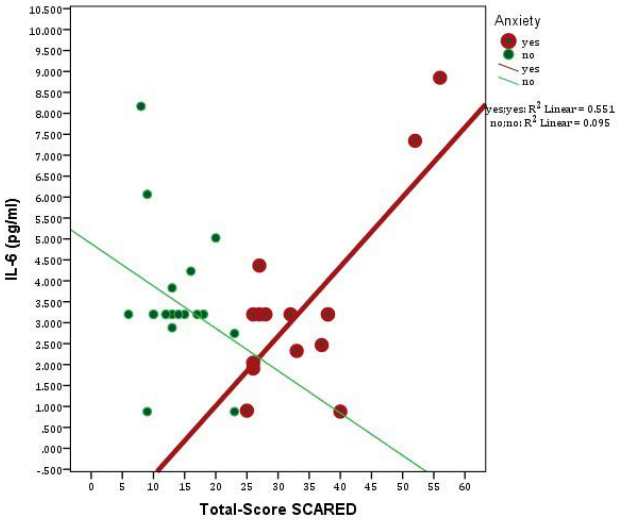

FIGURE 2. Linear regression between IL-6 and anxiety score

13 years or less, which has also been found in other studies throughout the specialty literature.

Regarding the distribution of anxiety by gender, we have not discovered any statistically significant differences in the studied lots (p = 0.665), and neither did other studies in the specialty literature reach a definitive conclusion as to which gender is more vulnerable to anxiety.[16]

The mother's level of education, correlated with the child's anxiety, was close to the threshold of statistical significance; however, the results of the first study that included a larger number of participants have reached statistical significance, suggesting that children from mothers with a higher level of education suffer from lower levels of anxiety than those from mothers with a lower level of education.

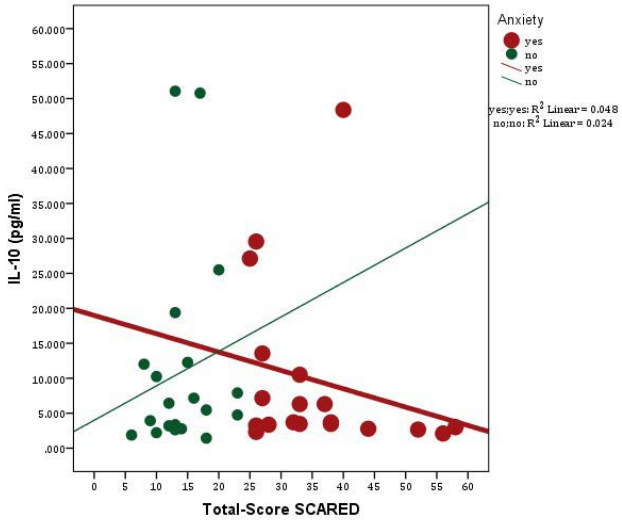

FIGURE 3. Linear regression between IL-10 and anxiety score

As far as we know, this subject has not been discussed yet in the specialty literature.

Age, the presence of a catheter, the type of pathology or the existence of siblings did not influence the level of anxiety. Although we have found no statistically significant data regarding their impact on anxiety, it is still important to pay attention to the siblings of pediatric oncology patients, as suggested by data in the specialty literature.

Correlations related to cytokine levels need to be interpreted restrictively because of the small number of enrolled patients. The mean values of IL-1β and the linear regression analysis carried out on the two lots have identified a significant difference between the group of anxious patients, who presented a positive correlation between the anxiety score and IL-1β serum levels, and the group of non-anxious patients, who presented a negative correlation between these two parameters. Recent studies indicate a marked increase in IL-1β levels in psychiatric disorders. A study of the protective role of probiotics which lower the levels of pro-inflammatory cytokines is under development.[17]

By studying the relationship between anxiety and serum levels of IL-6, we have identified a medium positive correlation in the anxiety group and a medium negative correlation in the non-anxious group. This has been previously described in certain studies, which discuss the key role of IL-6 in the pathogenesis of depression, with high detectable serum levels in such clinical scenarios.[18]

Regarding IL-10 levels, we have observed a difference between the two studied lots (anxious/ non-anxious), highlighting a low negative correlation between the anxiety score and IL-10 levels in the anxious group, as well as

a low positive correlation in the non-anxious group, with a statistical insignificancy. Similar data were reported by recent studies, which have described the protective role of IL-10 in anxiety disorders, describing low levels in anxiety and depression and high levels when no clinical signs of psychiatric afflictions are present.[19]

There was no correlation in the anxious group and a weak negative correlation in the non-anxious group between IL-12p40 levels and the anxiety score. The specialty literature reports low levels of this serum cytokine in anxiety or other psychiatric disorders, thus our results are in line with the ones from these studies.[20]

The evaluated serum levels of TNF-α were higher in anxious subjects compared to non-anxious patients. Recent studies show high levels of TNF-α in patients with psychiatric disorders as well.[20]

Correlations between the serum levels of C-reactive protein and the anxiety score of the two lots do not agree with the existing literature data, a fact owed to the small number of patients in the studied lot. Other studies have shown higher serum levels of CRP in anxiety disorders.[21]

CONCLUSIONS

Psycho-oncology is a relatively new medical field, thus very few scientific studies have been published in the last twenty years. Anxiety disorders are present during childhood and adolescence, and they have been found to be more prevalent in individuals with chronic illnesses, especially in pediatric oncology patients. In the oncologic population included in the present study, 4 types of anxiety were found, with a net predominance of separation anxiety, which was also most frequent in the <13 years age demographic.

Proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, presented high values in anxious subjects; on the other hand, IL-10 and IL-12p40 seemed to have low levels in psychiatric pathologies influenced by anxiety. CRP levels were not influenced by anxiety disorders.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

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