

The Evolution of Depressive Disorders in Children with History of Tuberculosis (Clinical Study in the Context of COVID-19 Pandemic in Romania)

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Abstract: *The Covid-19 pandemic has transformed the world since the beginning of 2020 and has produced many changes in key aspects of healthcare delivery. The emergence of SARS-CoV-2 has been seen as the promoter of many dramatic changes, especially in the medical field, having a huge impact on health systems around the world. Both patients and healthcare professionals have been subjected to a new stress factor that has resonated strongly in everyday life. This leads to an increased risk of association of psychological disorders, especially for patients suffering from chronic diseases, as they have already had a history of psycho-vulnerability. Patients with known chronic pathologies therefore have several concerns about important issues in the future, therefore, they are associated with an increased risk of occurrence of psychological phenomena. The present research represents an observational study, with a prospective case-witness type, carried out over a period of 2 years, between 2019 and 2020. The patients included in this research are part of the databases of the Children's Pneumology Department of "Sfantul Spiridon" Pneumoftiziologie Hospital of Galati and in the TB (Tuberculosis) Clinics in Galati County, being patients diagnosed and treated in these departments. We aimed to study the association between the presence of tuberculosis and depressive disorders reported in children aged 7-18 years, during 2019 and 2020 and in addition, to expose the results of the psychological effects of the pandemic on these chronic patients. We finally hypothesized that depression, but also the symptoms associated with them, will have a significantly higher incidence among patients with tuberculosis during the Covid pandemic.*

Keywords: TB, depressive disorders, COVID 19 pandemic.

How to cite: Mihailov, O., Loredana Matei, L., Ciubara, A.B., Dragostin, M., Mihailov, R., & Ciubara, A. (2021). Conspiracy Belief and Behavior in the COVID-19 Pandemic. How Belief in Conspiracy Theory Relates to Adherence to Quarantine Restrictions (Wearing Protective Equipment, Isolation, Hygiene) and Influences Antisocial Behavior such as Aggression and Selfishness, as well as Prosocial Behavior such as Help and Altruism. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, 12(2), 222-236. <https://doi.org/10.18662/brain/12.2/201>

Introduction

One of the main factors for which the year 2020 will remain in the common memory is represented by the pandemic caused by the SARS CoV-2 virus. Coronaviral infections have taken the entire medical community by surprise, overloading every component of this system (Luca, Baroiu et al, 2020). The numerous vulnerabilities were highlighted (Sandu, 2020a; 2020b), as well as the lack of elements of crucial importance for the medical system, a situation in which we were all confronted with the necessity to face many challenges (Alagna et al., 2020; Damian et al., 2020; Dara et al., 2020). Another extremely important change was the obligation to replace, as far as possible, the clinical examinations, respectively the “in person” meetings, with telephone consultations and to conduct various activities based on the Internet, in the virtual environment (Stop TB Partnership, 2020; Sandu, 2020c). At the same time, there has been information that, in many countries, the pneumonologists and experts in infectious diseases and public health (those involved in the prevention and care of Tuberculosis), together with ICU specialists, are or have been relocated to the front line to ensure the fighting against COVID-19 pandemic (Stop TB Partnership, 2020).

As for patients, their number has varied globally. The specialty literature confirms the existence of an upward curve of mortality detected among subjects, especially among the elderly and the patients who associate pre-existing comorbidities. The socio-economic consequences of this pandemic have had as direct implications the following: the contribution to the aggravation of the precarious situation in which many patients find themselves, the deepening of shortages, the appearance of malnutrition and of the morbidity and mortality related to this factor (Saunders & Evans, 2020).

Thus, at present, the medical world is focusing on two topics of main interest, both being the promoters of a relatively recent hypothesis, which has begun to concern more and more the medical community, namely:

- the effects of TB on the quality of life (QoL) of patients known to have this pathology, whether or not they associate concomitant COVID-19 infection; the analysis being performed before, during and after the anti-TB treatment (with the need for pulmonary rehabilitation);
- the potential offered by the increasing use of the Internet as a means of monitoring the patients for the performance of the proper management in TB's administration (Ngwatu et al., 2018).

Through manifold studies carried out, the specialized literature confirms the fact that mental illnesses had represented and continue to define a real health problem, with implications and consequences Worldwide (Luca et al., 2019, Burlea et al., 2012; Sandu & Damian 2018). From the strict point of view of the occurrences, the statistics confirm the fact that depression, as a psychiatric spectrum pathology, affects an impressive number of approximately 322 million people worldwide (WHO, 2017). Among patients with comorbidities, the prevalence of depression is even higher. Thus, for example, 26.8% of patients with hypertension and 8-18% of patients with diabetes also struggle with depression (Andreoulakis et al., 2012; Li et al., 2015).

Consequently, it will be admitted that both tuberculosis and depression share common risk factors, which explains, in part, the high prevalence of their comorbidity, the current reports ranging from 10 to 52% (Ambaw et al., 2015; Pachi et al., 2013; Yen et al., 2015). The interaction of these two pathologies is extremely complex, because there is a hypothesis according to which there is a causal relationship between the two pathologies. On the one hand, there will be an increase in proinflammatory cytokines characteristic to depression, which leads to decreased activation of the cellular and humoral immune system. This will ultimately contribute to the development of TB (Kiecolt-Glaser & Glaser, 2002). On the other hand, TB infection causes chronic inflammation, stimulating the release of pro-inflammatory cytokines that generate a series of cascading events. The enzymes at cerebral level, such as indoleamine 2,3-dioxygenase, which degrade the tryptophan and thus limit serotonin production, will initially be activated. Antituberculosis drugs can also play an important role in the development of psychiatric diseases. These include isoniazid, which has the ability to alter the absorption of serotonin, as well as high doses of ethambutol, whose presence has been associated with depression (Yen et al., 2015).

The key elements of the present clinical research are represented by the provision of support for maintaining an optimal state in terms of mental health, from the moment the patient is diagnosed with TB, until after its complete recovery. Another very important element, which is in itself a purpose of this paper, is defined by the desire to prove that psychological rehabilitation after healing the patient of respiratory pathology (TB) is a key factor in the fight against the so-called residual depression, as well as against the long-term decrease in the incidence of self-stigma and associated self-confidence issues.

Material and methods

The purpose of the research

The main characteristics of these patients were analyzed, focusing on the symptoms that indicate the existence of a depressive syndrome, based on the CDI (Children's Depression Inventory) questionnaire. The ultimate goal of this research was to demonstrate the null hypothesis that depression will be significantly more common among patients diagnosed with clinically manifest TB during the COVID-19 pandemic.

The Design of the Study Group

The present research possesses the characteristics of an observational study, with a descriptive character, which is based on a group consisting of a total number of 122 pediatric patients diagnosed with TB, monitored for a period of two years, between January 2019 and December 2020, respectively. The patients presented at the time of registration ages comprised between 7 and 18 years. All of them are subjects diagnosed and treated in the Children's Pneumology Department of "Sfântul Spiridon" Pneumoftiziologie Hospital of Galati and in the TB Clinics in Galati County. Prior to data collection, a written agreement was signed with the Ethics Commission of the above-mentioned medical units, as well as a confidentiality agreement for personal data processing, drawn up in accordance with Declaration of Human Rights of Helsinki. As criteria for inclusion in the study we mention: the age of the patients comprised in the previously mentioned interval, the signing of the informed consent (Sandu, 2020d) for inclusion in the study, patients with a definite diagnosis of TB.

For an easier understanding of the characteristics of these patients, we decided to subdivide the initial group into two equal groups, as follows:

- a group of patients with the diagnosis of Active Tuberculosis, diagnosed in 2020 (year of the COVID 19 pandemic) - consisting of a total number of 61 patients - considered the study group (subgroup A)
- a control group, consisting of subjects with a definite diagnosis of Tuberculosis received in 2019, the year before the COVID-19 pandemic – the control group (subgroup B)

Statistical analysis

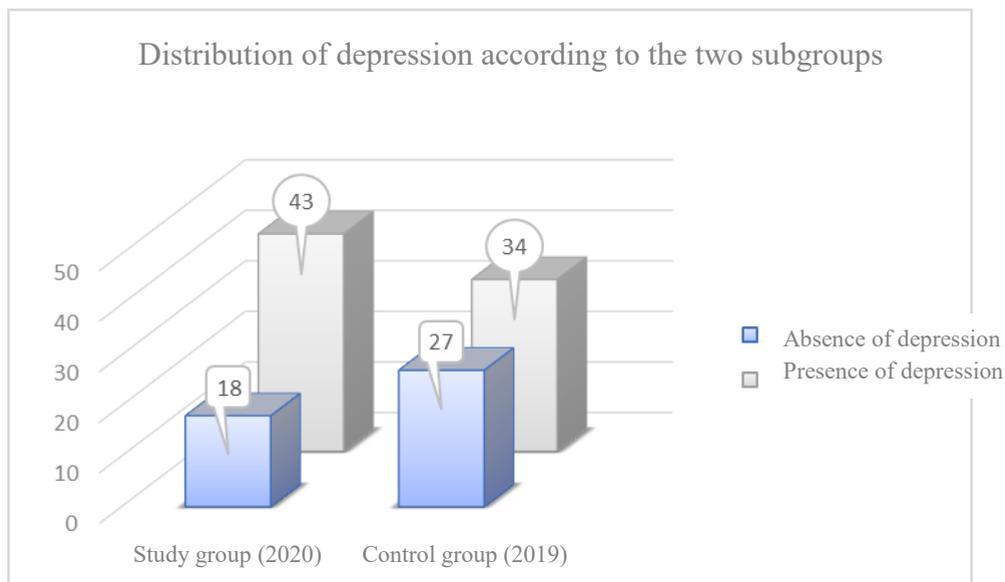
The statistical analysis is performed in a staged manner. Initially, the socio-economic and demographic, clinical-paraclinical and therapeutic information obtained from the medical records of the mentioned clinical units had been analyzed. Each of these data was entered in sampling lists,

then in summary tables to facilitate the final statistical analysis. Microsoft Excel v2020 was used as the work program, the database was corrected, labeled and accompanied by the outputs with all the final tables.

Results

We previously stated that the main group, consisting of a total number of 120 patients, was subdivided into two subgroups, depending on the years of diagnosis (2019, respectively 2020), each of the two subgroups comprising an equal number of 61 of patients. From the point of view of distribution according to the presence or absence of symptoms specific to depressive syndromes, it can be observed that at the level of the total group, the existence of a final number of 77 subjects (64.16%) diagnosed with depression was noted (according to the application of CDI questionnaire).

The distribution of the depression cases diagnosed in patients in the study group was also analyzed in terms of incidence in each of the two subgroups, the graphic image being exposed underlyingly. The predominance of cases of depression, regardless of the affiliation to the two subgroups, will be observed first of all, which is why we will issue the null hypothesis that patients diagnosed or undergoing specific treatment for TB pathology have an increased risk of depressive symptoms. Concomitant application of the chi-square test $\chi^2[\chi^2 = (77 - 55.5)^2 / 55.5 + (43 - 55.5)^2 / 55.5 = 11.14]$, had a final value higher than the reference value in the Fisher table, which is why we will continue with the rejection of the null hypothesis that there are no statistically significant differences between the two subgroups, by reference to the incidence of depressive phenomena. In this case we can conclude that depression has an increased incidence compared to the pandemic period.



Source: Authors' own conception

Thenceforth, we decided to perform the statistical analysis by reference to the age groups of the patients, in order to detect statistically significant conclusions, if any, according to the previous model. Thus, the patients were divided into 3 age groups, as follows:

- group I with ages comprised between 7 and 10 years: $n=17$, 22.07% from the total of the depression cases, 14.16% from the total of the group

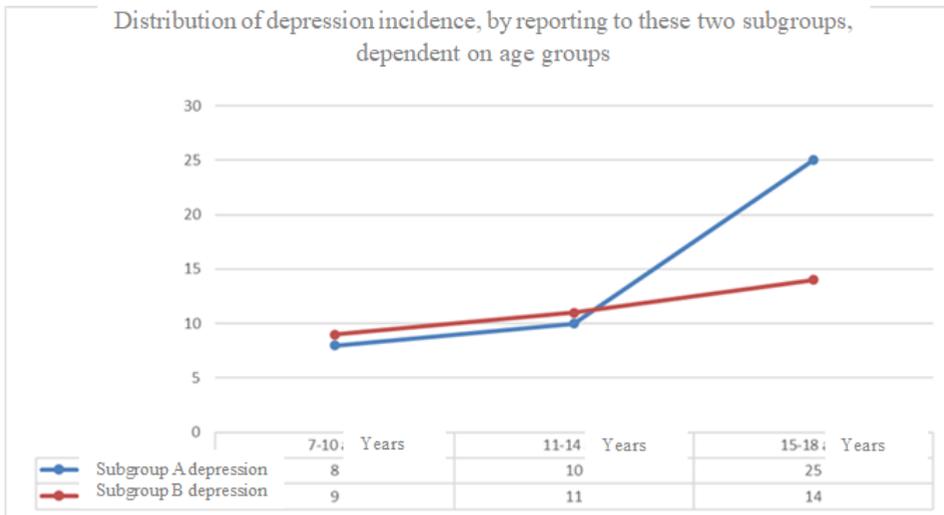
- patients with ages comprised between 11 and 14 years: $n = 21$, 27.27% from the 77 cases with depression, respectively 17.5% from the total of those 120 patients

- lastly, the patients with ages comprised between 15 and 18 years: $n = 39$ cases, 50.64% from the total of depression cases diagnosed according to CDI, signifying 32.5% from the total of the main group.

Thus, according to the information presented above, we will issue a series of null hypotheses as follows: it will be noted that, out of the total cases of depression diagnosed in the main group, the highest incidence will be reported in patients older than 15 years. Overall, a maximum incidence peak will be determined in subjects aged in the previously mentioned range, who belong to the study subgroup ($n = 25$, 32.46% among the depression cases).

Accordingly, from the point of view of statistical analysis with descriptive character, we will be able to issue, strictly from a quantitative point of view, the hypothesis according to which the incidence of depression presents an ascending curve, by reference to patients' ages (characterized by a relation of direct dependence). At the same time, it will be noted the influence of the pandemic on these distributions, with the predominance of cases in 2020, in the age group 15-18 years (with a percentage difference of 14.28%), while for patients under 15 years, it will be noticed that cases of depression predominate among those in the control subplot (with percentage differences of 1.29%, dependent on the age groups).

This fact is partly explained by the hypothesis that the impact of the pandemic was greater on the adolescents included in the study, due to the interdictions existing in pandemic context (isolation imposed to minimize community transmission of SARS CoV-2, the increase of on-call consultations, etc.).



Source: Authors' own conception

Another factor of increased importance in terms of the distribution of depression cases in pediatric patients diagnosed with TB, in and out of the pandemic context, is represented by the origin environments (but also the associated socio-economic conditions). The following will be observed:

- distribution approximatively equal of patient genders, in pandemic context, with the discrete predominance of those of female gender (n = 39, 50.64% out of the total of those 77 patients diagnosed with depression according to CDI)

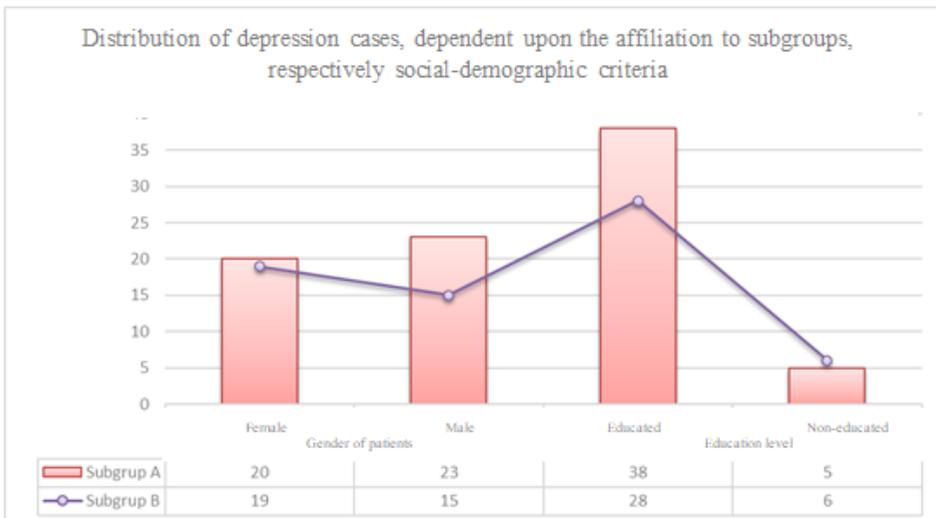
- the maximum incidental peak by concomitant reporting to the pandemic context and to the gender of the subjects is observed for those of male gender, diagnosed with depression in 2020 (n = 23, 29.87%, with a percentage difference of 10.38% as compared to the year 2019)

- 85.71% of the subjects known with depression (no matter the year of the diagnostic) are educated patients, the lack of education being present in extremely small percentage for pediatric patients with depression.

The concomitant application of the chi-square test aims to detect, if any, statistically significant differences in the incidence of depression (according to CDI) in pediatric patients, depending on whether they belong to one of the two subgroups:

A) Reported to the gender of patients: $\chi^2 = 46.71$ (female gender), respectively $\chi^2 = 46.31$ (male gender). In both cases the chi-square equation showed final values exceeding the reference limit according to Fisher table, which is why the null hypothesis that there are no statistically significant differences between the distributions of depression relative to the gender of the patients during the pandemic period will be rejected.

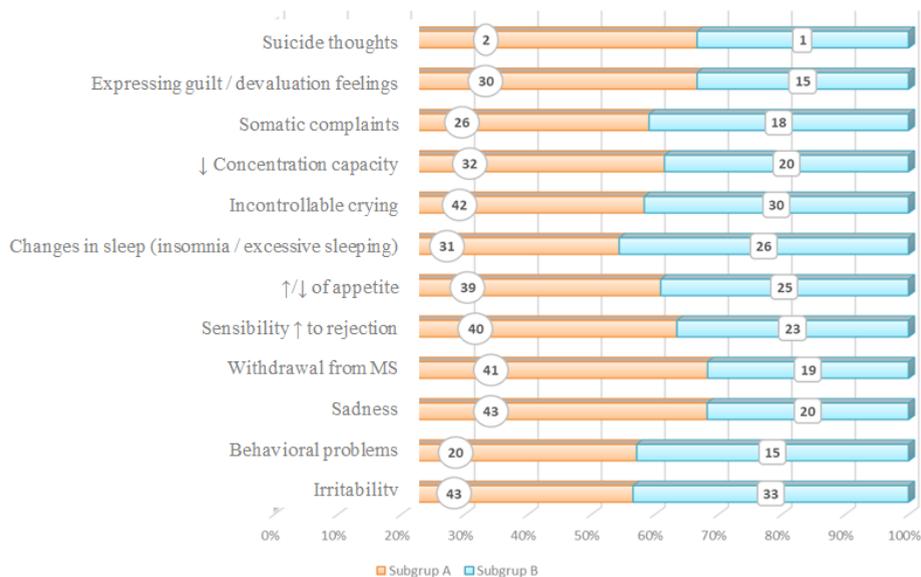
B) The education level presents values of the chi-square tests of 19.14 (for educated subjects), respectively 90.09 for those non-educated. It will be concluded that there are statistically significant differences, by reporting the distributions of depression in the pandemic, depending on the level of schooling of patients (increased incidence of depression in educated subjects, in a pandemic context).



Source: Authors' own conception

The image below shows graphically the distribution of symptoms associated with depressive phenomena, as detected by reference to the two subgroups analyzed. It will be concluded that the predominance of the symptoms appeared in a pandemic context, dominated by the existence of suicidal thoughts, the withdrawal from MS, by expressing the feelings of guilt / devaluation, respectively sadness.

Incidence of symptomatology associated to depressive phenomena, in pandemic context



Source: Authors' own conception

Discussions

The present clinical research demonstrated a prevalence of psychiatric depressive spectrum disorders diagnosed in pediatric patients known with TB of 64.16%. This value exceeds the data obtained by another study, conducted in three cities in Shandong Province from East China (58.6%) (Lei et al., 2016). Compared to the results obtained in other specialized studies, the prevalence of depressive phenomena was compared with those found in two studies conducted in Ethiopia (of 63.3%, respectively 67.6%) (Ayana et al., 2019; Tola et al., 2015). It should be mentioned that the prevalence of the present study is lower than that found in South Africa (81%) (Peltzer et al., 2012).

The variations presented above can be justified based on the differences in the design of the studies, by reference to the origin environments, the socio-economic characteristics, but also to the individual

variables. It is important to note in this situation that the pandemic caused by the new SARS CoV-2 virus had an important impact on the care of patients with TB (we are therefore discussing the delays in diagnosis, the decrease in the number of days of hospitalization, and the detection of severe increased general condition at the time of presentation, as well as the prevalence of psychological distress related to this population group) (Di Gennaro et al., 2021).

The specialty literature has confirmed through numerous studies that worldwide, the restrictions imposed by the pandemic context on the quality of life of patients (especially those under 18 years of age, diagnosed with TB) have had a significant impact on the depressive phenomena (Luca, Ciubara et al., 2020). According to international conclusions, the present study noted the increased incidence of depression in the year of the pandemic, year 2020 (55.84%). The presence of psychological distress can lead to a number of extremely serious adverse consequences, including poor results of the response to treatment (Ugarte-Gil et al., 2013), but also an increase in morbidity, mortality and at the same time in the risk of drug resistance (Wang et al., 2020). However, psychological stress can be alleviated by appropriate interventions (Kaliakbarova et al., 2013; Peddireddy, 2016). Therefore, it is essential for clinicians (pediatricians and pulmonologists alike) to explore effective intervention strategies.

From the point of view of socio-demographic characteristics, the present study detected the existence of statistically significant associations between the gender of patients and the incidence of depressive phenomena, a conclusion that will align with those obtained by specialized studies in Angola, but in contradiction with the conclusions of studies in Ethiopia (Ayana et al., 2019; Tola et al., 2015). It has been reported that the incidence of depressive disorders is increased among older patients (over 15 years old), fact justified in part by the hypothesis that older TB patients are an exposed group in terms of overall vulnerability, of increased mortality rates due to the risk of other comorbidities or of adverse reactions to the applied treatment (Peddireddy, 2016). In addition, the present study proved that education is a risk factor for the occurrence of depressive phenomena, a conclusion antagonistic to the research conducted internationally (Di Gennaro et al., 2020). According to other clinical research, the mental disorders have an increased incidence among patients with low educational levels (Ambaw et al., 2017). This population group, due to its educational level, may not have the ability to understand the characteristics of TB pathologies, of post-diagnostic emotional insecurity, or low literacy. Under these conditions,

these patients can easily be associated with psychological distress (Theron et al., 2015).

Conclusions

In conclusion, the prevalence of psychological suffering in pediatric patients with TB was high in a pandemic context, in Galati County. Finding such a diagnosis is therefore a stress factor, making psycho-vulnerable any patient, especially the pediatric subject. The educational level, the psychosocial reaction, the economic burden, the side effects of the psyche that appeared as a result of tuberculostatic medication, the severity of the self-assessed disease, the psychological consequences of the disease, all these are already known factors for detecting depressive phenomena in patients with TB. In addition, in the context of the COVID 19 pandemic, due to the restrictions imposed by it, the incidence of depressive phenomena has increased. The impairment of the family dynamics, the increasing of the need for psychological counseling, and stigma experienced by patients have been associated with psychological distress.

In a pandemic context, the aggravation or de novo appearance of mental health problems was detected, which, corroborated with the lack of screening programs for depressive disorders in children diagnosed with tuberculosis, lead to late diagnosis and decreased compliance with treatment, resulting in increased incidence of tuberculosis and many drug-resistant forms of the disease, associated with the depressive phenomena.

Therefore, the impact of the psychological stress on patients with TB must be acknowledged and, consecutively, effective interventions to mitigate this phenomenon should be developed. At the same time, more attention should be paid to those patients known to be at risk, with the ultimate goal of achieving better clinical outcomes and improving patients' quality of life.

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