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Neuroleptic Therapy as an Antitumor Protective Factor in Schizophrenic Patients with Polysindromic Framework: Observational Study

Leopoldo Ferrante[1, *], Walter Filippelli[1, *], Luigi Petrillo[2], Giovanni Castaldo[3], Alessio Sullo[1], Gaetano Motta[3], Anna D'Alessio[1]

[1]Department of Exercise and Wellness Sciences, Section Pharmacology University of Parthenope, Naples, Italy

[2]Villa Dei Pini Avellino - Psychiatric Clinic, Avellino, Italia

[3]ORL University of Campania L. Vanvitelli, Napoli, Italia

Email address:

Leopoldo.ferrante@unicampania.it (L. Ferrante), walter.filippelli@uniparthenope.it (W. Filippelli)

[*]Corresponding author

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Abstract: Schizophrenia is one of the psychiatric pathologies that involves the highest family, social and economic costs. The symptomatology affects various areas of an individual's life that include thought, emotions and the social aspect, with a remarkably long and variable course of the pathology, with subjects who may be chronically ill and others, instead, subjected to exacerbations and remissions. Despite the high efforts and advances in the field of pharmacology and psychotherapy treatments, to date, a real 'restitutio ad integrum' has not yet been reached. The drug therapy par excellence used to restore the biochemical balance is given by typical and atypical neuroleptics. The use of these drugs has led to widespread debates on the relationship between schizophrenia and cancer, as they appear to have an anti-tumor protective factor. In the Villa dei Pini Neuripsychiatric facility in Avellino, in a period between 2006 and 2016, an observational study was carried out on a population of patients diagnosed with schizophrenia (DSM-IV. TR). Each hospitalized subject, both new admission and re-entry, underwent clinical interview and a complete blood count with a chest x-ray. 4962 records of patients with Schizophrenic Psychosis have been taken into consideration, belonging to 888 patients (660 M and 228F) who had a history of being heavy smokers (about 90%) with concomitant depressive symptomatology (about 70%), hypertension (65%) and hearing loss (55%); the patients have been re-evaluated over time: at each re-entry into the clinic a complete blood count was performed with leukocyte formula, VES and PCR, and a Thoracic X-ray (the average number of patients returned to the clinic and 6 for patients 4 for female patients); some others were contacted by telephone interview. All the patients taken into consideration had at least one neuroleptic drug in therapy during the hospital stay. Among these patients, re-evaluated over time at each re-entry into the clinic or reached by telephone interview, about 2% (16 patients) developed lung K; the incidence is greater in patients with more than one comorbidity (diabetes, hypertension with familiarity due to oncological pathology). The data collected seem to go in the direction of the observations made by the various authors over time, that is the role of neuroleptic drugs as a protective factor in the onset and development of cancer, especially in the lung. To date the schizophrenia and cancer controversy is still open and in a phase of strong interest.

Keywords: Component, Formatting, Style, Styling, Insert

1. Introduction

Schizophrenia is a serious psychotic disorder that appears during adolescence or youth. Even if it is considered a single disease, it probably includes a group of disorders with heterogeneous etiologies, and this encloses patients whose clinical characteristics, response to treatments and evolution

of the disease result different. The signs and symptoms are variable and comprise alterations in perception, emotion, cognition, thought and behaviour. The expression of these manifestations is different for each patient and varies over time, but the effect of this condition is always severe and usually prolonged.

This disorder usually begins before the age of twenty-five. It persists throughout life and affects people of all social classes. Its symptoms can be episodic or chronic; positive symptoms (new and abnormal manifestations due to the disease itself) and negative symptoms (arising from the loss of abilities already present before the onset of the disease) are distinguished. On a therapeutic level, the new and old generation neuroleptics considered to be the first therapeutic option, as they are more tolerable and have positive effects on cognitive functions too. The relationship between schizophrenia and cancer has long been the subject of psychiatric controversies.

This data is supported by the lack of conclusive empirical evidence on the occurrence of tumors in schizophrenic patients [53-61-62]. In 1978, Achterberg and others showed that only 1% of all schizophrenic patients died of cancer [59]. In 1929, White found a 13% incidence of cancer in “schizophrenic paranoids” and only 4% in “schizophrenics”. In contrast, Craig & Lin found cancer death rates of similar ages in patients compared to the general population [60]. Still in 1979, Rice stated that bronchogenic carcinoma had never been observed in chronic long-term schizophrenic patients, despite their heavy tobacco intake [20]. This observation is supported by Craig & Lin (1981), who found a low incidence of lung carcinoma [60]. In light of these evidences, it would be of considerable interest to demonstrate a different recurrence of cancer in such patients, who are subject to peculiar experience and conditions that could modify the cancer itself.

2. Epidemiological Considerations: Ratio

Studies that addressed the relationship between mental illness, especially schizophrenia, and prevalence and cancer mortality gave different answers. These studies can be divided into three main groups [6-7]. In the first group of studies, between the 1930s to the mid-1970s, prevalence and cancer mortality in patients with severe psychiatric disorders was almost always lower than in the general population [8-19]. This data seemed very reliable especially in the case of lung tumors [20-21], but at least one study indicated it with stringent certainty in relation to any neoplastic location [22]. A second group of studies, largely subsequent to the previous ones, did not confirm these results. indicating in schizophrenic patients, again with respect to the general population, an incidence or mortality from cancer that is not lower and indeed often even higher. In addition, these studies have criticized previous studies in various ways [23-30]. Baldwin, for example, stated that “the assumptions of incompatibility or rarity of various diseases in schizophrenics - see tumors, epilepsy, allergy, diabetes and myasthenia gravis - derive from interpretations of clinical 'non-experiences' based on impressionistic overestimation) of what depends on the case " [7]. And in fact, even against non-neoplastic diseases, the hypothesis of a greater "resistance" of schizophrenic patients has been repeatedly criticized [31-32]. More in detail, it was pointed out that the studies with results in favor of this hypothesis used insufficient epidemiological methodologies, for example by resorting to proportional rather than absolute mortality, or by excluding some types of cancer (brain tumors, sarcomas) [7]. Taken together, the main merit of these criticisms consisted in underlinig the extreme difficulty encountered in carrying out studies of this kind in a truly rigorous manner. Extremely large samples of the schizophrenic population (at least 100,000 patients per year) should in fact be examined, and even before that it is necessary to respect homogeneous and reliable criteria for the diagnosis of both schizophrenia and neoplasia, without neglecting elements such as age, sex, the pharmacological therapies in place and the greater or lesser exposure to the main risk factors for cancer [33-35]. It may be remembered, for example, that there a tendency not to diagnose many cases of cancer in schizophrenic patients because they have a higher pain threshold and a low propensity to communicate somatic illnesses, and also because it exists in psychiatric hospitals a lesser habit of carrying out autopsies. However, it has also been observed, in the opposite sense, that criticisms of this kind sometimes seem to derive more from a general reluctance to consider plausible the hypothesis of a reduced incidence of cancer in schizophrenics than from a precise and impartial examination, for each single investigation., of the difficulties and inaccuracies really at stake [6]. However, in addition to these study groups there is a third. This is a category of studies, some very recent, in which a significant difference in mortality from cancer in people with psychiatric pathology compared to the general population was not highlighted [36-42]. This data, compared to the previous ones which highlighted, respectively, a lower or a higher mortality from cancer in schizophrenic subjects, seems to be the most reliable, although in general the conclusion is more probable, considering the discrepancy of the results that emerged from the complex of the three groups of studies, is that of the absence of a constant pattern of cancer mortality in schizophrenic patients [30]. In confirmation of the impossibility of extrapolating a unique and constant evidence applicable to any schizophrenic individual, and therefore referable to schizophrenia itself, it is interesting to note that some factors adduced to justify the hypothetical lower mortality from cancer in schizophrenics are the same as in question to justify the opposite hypothesis. This is the case, for example, of the pharmacological factors, invoked both by the supporters of a lower mortality, who hypothesize the antineoplastic activity of some neuroleptics (chlorpromazine, haloperidol and others) [45-51], and by the supporters of a higher mortality, who instead call into question the increase in prolactin levels caused by many neuroleptics and therefore the increased risk of breast cancer [6-40-52-53]. The latter,

however, is a fact that has not always been confirmed [19-44]. Instead, a less marked ambiguity affects the role of the so-called environmental factors, which are cited by those who support the hypothesis of a lower mortality from cancer in schizophrenics, as the eventual institutionalization, or alternatively rehabilitation regimes, would reduce exposure to environmental carcinogens (cigarette smoke, alcohol, poor diet)[6-7]. Those who, on the other hand, argued that, despite the restrictive and therapeutic measures, schizophrenic subjects are more exposed to environmental carcinogens such as cigarette smoke and alcohol, and that for this reason they would have a higher mortality from cancer, collide with a important data. In fact, schizophrenic patients, precisely because they are usually more exposed to this kind of risk factors, actually show a lower incidence than expected, as they have a lung cancer mortality almost equivalent to that of the general population [55]. Ultimately, the factors called into question only by the supporters of the hypothesis of a reduced incidence of cancer in schizophrenic subjects are of two types: biological-genetic and psychological. Among the genetic hypotheses we can mention that according to which both cancer and schizophrenia depend on a respective predisposing hereditary polygenic constellation, against which various environmental factors would then carry out a trigger action [1]. It would therefore be extremely difficult for both polygenic constellations to occur in the same individual, so that the respective pathologies, schizophrenia and cancer, would tend to be mutually exclusive. Other hypotheses, always of a biological-genetic setting, concern the possibility that schizophrenic subjects are "protected" against cancer, now for a deficiency modification of the enzyme methionine adenosyl-transferase [56], now for a more intense antitumor activity of the lymphocytes [57]. Both of these peculiarities, in fact, derive from a genetic determination. There is also a different and more complex hypothesis, based on a study that found a higher incidence of cancer in schizophrenic subjects (especially of the lung and pharynx), finding, on the contrary, a reduced incidence in non-schizophrenic twins and family members. non-schizophrenics. The authors of this study suggest, beyond the greater exposure of schizophrenic subjects to environmental carcinogens (cigarette smoke, alcohol), the existence of a genetic risk factor for the development of schizophrenia, a factor which, in family members who do not develop this disease, would carry out a protective action against carcinogenesis [58]. As for the psychological hypotheses, for example, the rigid defense mechanisms that characterize schizophrenia have been invoked, as they could reduce the immuno-suppression usually resulting from stress [59]. More generally, it has been hypothesized that the denial of the most disorganizing emotions, in cases where this is expressed in the so-called schizophrenic autism, would exclude different expressive modalities, the main one being, according to some authors, the onset of cancer. [60] Finally, as already mentioned, psychoanalytic theories of the psychosomatic field also argue that deep and poorly mentalized anxieties, if not managed by defending themselves through delusional psychic modalities, could mobilize archaic defensive reactions of a somatic type, such as cancer. Evidence has recently emerged, based on accurate epidemiological studies, that some mental diseases, whose biological substrate has so far been recognized, may be associated with a persistent viral infection; in fact, two serological studies demonstrated a remarkably high titre of IgM-type and IgG-type anti-cytomegalovirus antibodies in the cerebrospinal fluid of patients with schizophrenia. Cytomegalovirus, due to its characteristics of producing a persistent and latent viral infection and causing lesions of the nervous system during acute infection, would have the requisites to be a good candidate for the etiology of these mental disorders [69]. Treatment with antipsychotic medications may result in a decrease in CMV antibodies, while treatment with anti-herpes virus and anti-inflammatory medications may reduce symptoms in some individuals with schizophrenia. There is also some overlap in the genes that are thought to operate in CMV infections and schizophrenia. The strongest argument against the role of CMV in schizophrenia is the absence of the traditional CMV neuropathological changes in the brains of individuals with schizophrenia; however, neuropathological studies of CMV have mostly been conducted in immune-compromised individuals [70]. Although several studies indicated a possible increase in apoptotic susceptibility, accumulating evidence suggests that apoptotic activity may actually be downregulated in chronic schizophrenia. Furthermore, antipsychotics produce complex effects on apoptotic regulation in the central nervous system, activating both proapoptotic and antiapoptotic signaling pathways [72]. The recent development of high throughput compound screening has allowed drug repurposing to emerge as an effective avenue for discovering novel treatments for cancer. A correlation has been found that patients treated for schizophrenia have lower incidences of certain types of cancer, such as respiratory, prostate, and bladder cancers. These compounds have also been shown to inhibit cancer proliferation in a variety of cancer cells, including melanoma, lung carcinoma, breast cancer, pancreatic cancer, glioma, and prostate cancer, among others. Antipsychotic drugs induce apoptosis and suppress metastasis in vitro and in vivo models through mechanisms involving p53, STAT3, STAT5, protein phosphatase 2A, cholesterol homeostasis, integrins, autophagy, USP1, wnt / β-catenin signaling, and DNA repair.

3. Materials and Methods

The study was conducted on a population of subjects diagnosed with schizophrenia (DSM-IV. TR) recruited at the Neuropsychiatric nursing home Villa dei Pini in Avellino. 4962 records of patients with Schizophrenic Psychosis – admitted from 01-01-2006 to 31-12-2016 – have been taken into consideration, belonging to 888 patients (660 M and 228F) who had a history of being heavy smokers (about 90%) with concomitant depressive symptomatology (about 70%), hypertension (65%) and hearing loss (55%); the patients have been re-evaluated over time: at each re-entry into the clinic a

complete blood count was performed with leukocyte formula, VES and PCR, and a Thoracic X-ray (the average number of patients returned to the clinic and 6 for patients 4 for female patients); some others were contacted by telephone interview.

Each patient was evaluated for admission by clinical interview, paying particular attention to the collection of the following information: age, gender, marital status, schooling, years of diagnosis, longitudinal comorbidity (including substance abuse), smokers, familiarity for psychiatric disorders in first-degree relatives. The concomitant presence of depressive symptoms was verified retrospectively through a clinical record with the CDSS (Calgary Depression Scale for Schizophrenia) > 6 out of the 9 items on the scale. At each hospitalization, every patient was given a complete blood count with the leukocyte formula, VES and PCR, and a chest X-ray. The patients were re-evaluated over time at each re-entry into the clinic with complete blood count with leukocyte formula, VES and PCR, and a Chest RX. All the patients considered had, during the hospital stay (average hospitalization of 42 days) at least one neuroleptic drug in therapy.

4. Results

All the patients taken into consideration had at least one neuroleptic drug in therapy during the hospital stay. Among these patients, re-evaluated over time at each re-entry into the clinic or reached by telephone interview, about 2% (16 patients) developed lung K; the incidence is greater in patients with more than one comorbidity (diabetes, hypertension with familiarity due to oncological pathology).

5. Conclusions

The relationship between schizophrenia and cancer has long been the subject of controversy among psychiatrists, which has been supported by the lack of conclusive empirical evidence on the occurrence of tumors in schizophrenic patients compared to the general population: schizophrenics therefore represent a subpopulation that offers the opportunity to study the recurrence of cancer in the presence of a specific pharmacological treatment with neuroleptics. All patients taken into consideration, as already mentioned, had at least one neuroleptic drug in therapy during the hospital stay. About 90% of patients had a smoking status in the medical history and the majority of them had a concomitant depressive state aggravated by hearing loss. Depression is not a risk factor for the appearance of cancer at all; there is no doubt that chronic depressives with a clinical picture aggravated by bilateral sensorineural hearing loss that, due to hearing and communication deficits, predisposes to a loss of interest or integration skills, have a higher risk of developing cancer than non-depressed people or those with a single episode of depression. Another well-known vulnerability factor is tobacco in association with depression. Haloperidol, one of the most used drugs in the treatment of schizophrenia, is an inhibitor of dopamine D2 receptors and in this way it regulates the pathway of the kinase A protein activated by the cyclic AMP, ultimately regulating also the transcription factor CREB involved in numerous cellular functions. The study of the molecular interactions of Haloperidol highlighted the interaction of the drug with molecules involved in apoptosis (caspase 3 and Bcl2), kinases involved in various cellular processes such as proliferation and differentiation (Akt, Erk ½), fundamental growth factors also in the process of angiogenesis (FGF, VEGF). Di Chiara and others showed that the Haloperidol metabolite II exhibits antiproliferative properties at micro molar concentrations that induces apoptosis in various types of cancer. Although the presence of other "protective" factors in this subpopulation cannot be excluded, taking into account the multifactoriality underlying the appearance and development of cancer, such evidence has led us to hypothesize a role of pharmacological treatment of schizophrenic patients in prevention incidence of lung cancer.

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