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Neurodevelopment or neurodegeneration: Review of theories of schizophrenia

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Many hypothesis have tried to explain the aetiology of schizophrenia, the abnormal neurodevelopmental hypothesis is one of the most widely acknowledged and is based on the presence of both prenatal and perinatal disorders, differences in IQ or the existence of genetic abnormalities, which, with the interaction of certain environmental factors, schizophrenia could occur at some point in the development. This hypothesis provides a good account of how these factors result in an alteration in the normal development and how they can lead to a disorder of schizophrenia. On the other hand, a smaller but not insignificant number of studies based on variables such as the presence of neurotoxicity in the brains of individuals with schizophrenia, alterations at the structural and brain connectivity, suggest the existence of a degenerative process in the course of this disease. In this work, we review the different factors underlying both hypotheses, some of which are difficult to categorize in either approach given the controversy and lack of consensus in their interpretation of the available data. Finally, we discuss the need for a non-exclusive alternative model to help understand the available evidence on the origin, course and consequences of the disease.

Keywords: Schizophrenia, Abnormal neurodevelopmental hypothesis, Neurodegeneration hypothesis, Psychosis

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Neurodesarrollo o neurodegeneración: Revisión sobre las teorías de la esquizofrenia

La etiopatogenia de la esquizofrenia ha sido explicada por diversas teorías. La hipótesis del neurodesarrollo anormal se basa en la presencia de alteraciones tanto prenatales como perinatales, diferencias en el coeficiente intelectual, o la existencia de anormalidades genéticas, que al interaccionar con ciertos factores medioambientales, hacen que el trastorno esquizofrénico se manifieste en algún momento del desarrollo. Esta teoría es muy bien acogida por la comunidad científica ya que explica muy bien cómo estos factores dan como resultado una alteración en el desarrollo normal y como pueden derivar en un trastorno de esquizofrenia. Por otra parte, una cantidad menor aunque no menospreciable de estudios sugiere la existencia de un proceso degenerativo y se sustentan en variables como la presencia de neurotoxicidad en los cerebros de individuos con esquizofrenia, las alteraciones estructurales y de conectividad cerebral. En este contexto se revisan los diferentes factores subyacentes a ambas hipótesis, donde algunos son difíciles de catalogar en uno u otro enfoque dada la controversia y falta de consenso en los datos. Finalmente se discute la necesidad de adoptar un modelo alternativo no excluyente que ayude a comprender la evidencia disponible sobre el origen, curso y consecuencias de la enfermedad.

Palabras clave: Esquizofrenia, Neurodesarrollo, Neurodegeneración, Psicosis

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INTRODUCTION

The etiology of schizophrenia as a mental illness has been subject to interest since the early 20th century. Authors such as Bender[1] or Watt[2] were among the first to provide data on abnormal neural development prior to the appearance of the condition. Advances in research techniques and an increasing interest in neurobiology, genetics, and neurogenesis both in normal and pathological development, have helped to build up in-depth knowledge of neural anomalies in patients with schizophrenia, generally attributed to abnormal neurodevelopment. A large number of studies from different areas of research consider this theory to explain the data obtained, for example: a) the increase in the prevalence of schizophrenia in interaction with certain prenatal and/or perinatal factors, such as obstetric complications or complications during pregnancy; b) genetic conditions resulting in an abnormal expression of certain neuronal processes, such as a neuronal migration or synaptogenesis or abnormal axonal growth; c) the presence of certain minor physical abnormalities in patients with schizophrenia, such as a smaller cranial circumference, ojival palate, low set ears and dermatoglyphs; and d) different alterations emerging over the course of the individual's development, and a shortage of certain social and cognitive skills.

Despite this, there are several aspects of the illness that are not explained by the theory of abnormal neurodevelopment. In fact, in one of the earliest definitions of schizophrenia, "dementia praecox,"[3] Kraepelin already stressed the degenerative aspects of the condition. The neurodegenerative processes in patients with schizophrenia are clearly seen in studies on the presence of neurotoxicity, morphological alterations in the brain (such as the reduction of the frontal and temporal lobes and the enlargement of the ventricles), and the fact that antipsychotic medication appears to slow down the progress of the disease, are examples that support the theory that schizophrenia follows a degenerative process.

Despite advances in research thanks to neuroimaging techniques and genetic studies, among others, at present, there is still no conclusive theory regarding the origin of schizophrenia. In order to clarify the extent to which the two hypotheses described can explain the etiopathogenisis of the condition, we examine the most relevant data collated by them in order to attempt to clarify this complex matter.

HYPOTHESIS OF ABNORMAL NEURODEVELOPMENT

The model of altered neurodevelopment proposes that the evolution of schizophrenia is diachronic. In this way, the individual is born with certain genetic factors that, in interaction with certain environmental factors, prevent the brain from developing normally, and at a given time, the person may be affected by the external and internal factors that trigger the onset of the condition.[4,5] In this way, this double impact hypothesis suggests that the action of an early deleterious factor affects neurodevelopment, creating a vulnerability to a later, subsequent action of secondary impact. It is the latter that causes the damage resulting in the psychotic condition itself. It is never sufficient to have just the first or the second; both variables must work together.[6] According to this theory, biological alterations and other characteristics of the illness would be present in the patient well before the onset of the characteristic symptoms of this pathology, but they would not be present until a certain level of development is reached, upon interacting with certain external factors.

Prenatal and perinatal alterations

In 1988 a study was completed in which it was observed that there was an increase in prevalence of schizophrenia in children born to mothers in the second trimester of pregnancy during the 'flu epidemic of 1957,[7] and in babies born to mothers who had contracted rubella during pregnancy.[8] The season of birth also appears to affect subsequent development of this condition, as it was observed that schizophrenia is between 5 and 8% more common in individuals born in the spring and winter compared to other seasons.[9]

Similarly, place of birth appears to determine the appearance of the illness given that there is a significantly positive relationship between the size of cities of birth and the frequency of schizophrenia and other psychotic conditions, which are more prevalent in larger cities.[10]

Several studies have been conducted on the connection between obstetric complications and schizophrenia observing that individuals suffering some kind of difficulty during birth such as hypoxia, a complex caesarean section, premature labor or Rh incompatibility, are more likely to develop schizophrenia.[11,12] However, the numerous papers that question the predictive value of these findings should also be taken into account.[13-15]

Developmental alterations

The presence of certain minor physical abnormalities in individuals with schizophrenia is another one of the factors upholding the hypothesis of abnormal neurodevelopment as these alterations, which tend to be of little physiological or aesthetic consequence, occur during the first trimester and early second trimester of pregnancy, the main period of development in the fetal brain. Furthermore, these malformations are caused by an alteration in the ectodermis,

suggesting that they share their embryonic origin with the brain.[16] Several meta-analyses have been completed regarding these malformations,[17,18] highlighting issues such as a smaller cranial circumference at birth, and the possible existence of delayed brain growth,[19] low set ears[20], a highly arched palate, a grooved tongue, epicanthus, cleft palate, telecanthus and a wide gap between the first two toes.[18]

A large number of follow-up studies have identified greater frequency of certain delays in child development and lower social function and general intelligence in children who go on to develop schizophrenia.[21-23] It is worth noting motor skill dysfunction as one of the most consistent findings in studies on the background to schizophrenia, which can distinguish between children and/adolescents who later develop schizophrenia.[24,25]

Other alterations observed in individuals with schizophrenia that appear during the course of development are: intelligence quotient (IQ), which has been described as lower in children who later present the clinical symptoms of schizophrenia in comparison with other healthy individuals,[27] although this evidence is not entirely conclusive. Several studies suggest that there is a drop in intellectual quotient during adolescence, while others conclude that performance is greater in individuals close to suffering a psychotic episode, or that IQ deteriorates during the transition to psychosis.[27,28] Nevertheless, it should be stressed that IQ does not appear to fall outside normal ranges in individuals who later develop schizophrenia and that the differences resulting from a comparison with unaffected subjects are minor. In this way, taken alone, the predictive value of IQ is modest, effective in only 3% of cases of schizophrenia.[29]

Neurochemical alterations

The development of the brain depends on sequential processes that are highly complex and organized, meaning that any complication occurring in the initial stages of development may result in huge abnormalities at subsequent stages. In schizophrenia, it has been reliably proven that there are alterations in some specific molecular signals involved in cell formation and organization, and therefore, the structure and function of the brain. For example, a shortage of post-mortem tissue reelin expression has been observed in patients with schizophrenia. This is relevant as reelin is a protein that guides certain neuron clusters to the appropriate place in the brain and is released at intense levels during neuron migration.[30,31] Furthermore, a reduced appearance of polysialic acid (PSA) has been observed on the neural cell adhesion molecules (NCAM) in patients with schizophrenia. This molecule is involved in axonal growth, the synaptogenesis of interneurons and the formation of inhibitor circuits related to the condition.[32,33] It has also been considered for some time that the proteins involved in the condition include: the brain-derived neurotrophic factor (BDNF),[34] the glial cell-derived neurotrophic factor (GDNF)[35] and the epidermal growth factor (EGF).[36]

Genetics and environment

We can affirm that genetics, neurodevelopment and schizophrenia are inextricably linked.[37] All the molecules involved in neurodevelopment, such as those mentioned above, are controlled by specific genes relating to development and with the pre- and post-natal maturing of the brain.[38,39]

Inheritability in the pathogenesis of schizophrenia is estimated at between 70% and 85%.[40] Numerous connections have also been discovered between schizophrenia and certain genes such as neuroregulin 1 (NRG1),[41,42] dysbindin,[43] el DISC-1[44], proline deshydrogenase[42,45] and the regulator of G protein signaling 4 (RGS4)[40], thus confirming the idea that schizophrenia is not determined by a single gene. But although the etiology of the illness must take genetic factors into consideration, around 60% of those affected have no first or second degree relatives with this disorder and furthermore, the degree of concordance for schizophrenia between identical twins is only 50%.[40,46]

Given that the hereditary factor alone cannot explain the etiology of schizophrenia, research has been conducted into the role of environmental factors. Examples of these factors are those previously mentioned regarding pre- and perinatal alterations, such as infections, time of birth and obstetric complications.[40] Additionally, stress,[48] substance abuse - cannabis and other drugs,[49] social adversity during childhood and/or adolescence,[50] social exclusión,[51,52] are circumstances that may create a predisposition to psychosis in vulnerable individuals.

Alterations in neurocognitive functioning

Unlike other symptoms, cognitive symptoms in schizophrenia may reflect the evolution of the illness, insofar as if there were a degenerative process in the brain in schizophrenia, the cognitive decline of patients would be clearly observable (e.g. progressive reduction in capacity for attention/concentration, memory, language, etc.). However, studies on the progressive course of the disease are not conclusive, and although a pattern has been suggested recently through clinical stages[53] the connection with the effect on different cognitive functions in schizophrenic patients is as yet unknown. Available data is ambiguous and does not seem to clearly support the hypotheses of either neurodevelopment or neurodegeneration. This dilemma is described in depth in the results obtained by a recent meta-analysis by Napal et al.[54] These authors completed a separate

analysis of cross-sectional and longitudinal studies and compared groups of patients at different stages of the condition: high risk (HR), first psychotic episodes (FPE) and chronic schizophrenia (CS). They found that depending on the type of study completed the results showed a progressive deterioration in cognitive functions, in the case of cross-sectional studies, or a stabilization of the deterioration after the onset of the illness, in the case of longitudinal studies. There are many studies showing that FPE patients have a poorer cognitive performance than those in the HR category, and at the same time better than patients with CS.[55-58] However, those studies that perform a follow-up of the same patients over a number of years show that the deterioration observed is not progressive.[59,60] Overall, studies on the matter appear to show that there is a general cognitive deficit in all areas and although it is not possible to define a characteristic profile of cognitive deterioration in schizophrenia, it is already evident in the prodromic phase of the condition.[54] Meta-analytical studies on cognition prior to and during the initial phases of the illness coincide in that attention, memory and executive functions are further deteriorated than in control patients.[61,62] There are many limitations when studying the course of cognitive deterioration in schizophrenia, such as the influence of medication, heterogeneity of symptoms and the evolution of the illness, the variety of methods and analytical tools used to measure cognition, etc.

HYPOTHESIS OF NEURODEGENERATION

This hypothesis focuses on the fact that schizophrenia is characterized as being a chronic and progressive disorder of the nervous system, resulting in biochemical changes that lead to different clinical syndromes, affecting the loss of neurological function and the deterioration of behaviour.[63]

Psychosis almost always emerges in late adolescence or early adulthood, generally between the age of 18 and 25, when the prefrontal cortex is still developing. We still do not understand all the changes in normal cortex development in this period, and therefore they are not clear with regard to schizophrenia. Upon examining the clinical course of the illness, it can be seen that some patients have a chronic course, with a probability of deterioration in correlation with the number of periods and the duration of positive symptoms.[64] A static course is uncommon in schizophrenia, and improvement is even less common. Sustained recovery occurs in less than 14% of patients, generally within the first five years after a psychotic episode.[65]

Structural alterations and alterations in brain connectivity

Several morphological studies support the presence of changes in the brains of patients with schizophrenia that may be reflecting the degenerative effect of the condition on the brain. One of the most significant findings is a reduction in the temporal lobe, seen in 74% of studies completed using functional magnetic resonance (FMR).[66,67] The volume of the frontal lobe has also been observed to be different, with affected individuals showing a smaller volume compared with control patients, as observed in 59% of the studies reviewed.[68] Other studies on patients with schizophrenia show that they had a smaller hippocampus than healthy individuals of the same age, and that the reduction in volume was greater in elderly patients than in young patients.[69] In a meta-analysis of longitudinal studies completed by Shenton et al. differences were also observed in areas such as the hippocampus, basal ganglia or cavum septum pellucidum in healthy individuals and patients with schizophrenia over time.[70] Longitudinal studies have also shown that there is an annual reduction in the thalamus of 7% in adolescents with schizophrenia.[71] Considerable reductions in the size of these areas of the brain indicate a loss of white and gray matter in patients with schizophrenia. This, together with enlargement of the ventricles, constitute the most consistent findings in literature on the topic.[72] An increase in the lateral ventricle was observed in 80% of studies, together with an enlargement of the third ventricle, observed in 73% of studies.[73] These differences have been located recently in initial psychotic episodes and also in patients with early onset of the illness, suggesting that the degenerative process commences from the earliest stages of the disorder.[72-74]

Brain gliosis is another indicator of neuron degeneration as this type of cells responds to certain neuron injuries and is observed in brains with neurodegenerative disorders. Post-mortem examinations show an absence of gliosis in patients with schizophrenia,[75] which would suggest the hypothesis of neurodegenerative is incorrect, however, the results are not conclusive. In a recent review of post-mortem studies completed by Schneider et al. there were differences observed, although not conclusive, in astroitosis and microgliosis in schizophrenic brains. They conclude that the positive findings must not be underestimated, as both types of gliosis are common in the autopsy of brains, above all from middle age onwards, making it necessary to perform more studies on younger patients.[76] The data appear to be clearer with regard to another type of glia, oligodendrocytes. It seems that this type of gliosis is observed in schizophrenia[77] and can be interpreted as an altered response to a pathological process in the brain. Bartzokis et al. suggest that the altered mechanism observed in the myelination process in schizophrenia may be the trigger for the loss of white matter in the prefrontal cortex.[78] This myelination is performed by glial cells such as oligodendroglia mentioned above, in order to maintain and strengthen axons and connections.[72,78] These authors also sustain that a reduced formation of inhibitor synapses and excessive shortening of excitatory synapses over the course of the illness may be responsible for the loss of gray matter

observed in schizophrenia, above all in the frontal lobes, and the imbalance found between excitation-inhibition in the pre-frontal cortex.[72] These data support the hypothesis of neurodegeneration as this shortening is a form of degeneration, retraction or excessive excretion of axons.[79] Another mechanism that would explain progressive degeneration in schizophrenia is diminished neuroplasticity, a deterioration of activity in the dendritic spines and synapses, where the force of transmission is weakened due to poor connections and a reduction in dendritic spines, resulting in a loss of neuropil (dense cluster of axon, dendrites and glial cell processes).[80] There must be a slight form of apoptosis in the dendrite processes and individual synapses, causing the disappearance of synapses and the reduction in size of the neuron some without causing death of the cell.[72,81]

Stressing the idea that schizophrenia is a connectivity disorder, several studies highlight an alteration in the *Default Mode Network* (DMN), which can be defined as the baseline for neuron activity, with the patient is at rest, and not focusing on any specific purpose.[82] It has been proven that DMN is clearly related to schizophrenia where there is a disconnection, disintegration and de-synchronization of the network in comparison to healthy individuals,[83] just as occurs in degenerative diseases such as Alzheimer's, where the lack of DMN integrity is a biomarker for brain protein deposits, to which the network is particularly sensitive.[84,85]

Chemical Alterations

One of the variables on which the hypothesis of neurodegeneration is based is the presence of chemical alterations.[86]

It has been shown, for example, that dopamine is involved in the processes of proliferation, migration and pruning, as well as the processes of oxidative stress excitotoxicity that cause neurodegeneration.[87] Although the dopamine hypothesis was widely recognized due to the high concentrations found in patients with schizophrenia and the response observed to certain antagonist drugs, this was insufficient to clarify the etiology of schizophrenia.

In recent years more weight has been given to studies on N-methyl-D-aspartate receptors (NMDA). These receptors are involved in the neurotransmission of glutamate and it seems that NMDA receptor dysfunction results in very similar symptoms to those seen in schizophrenia, as seen in the administration of antagonists such as ketamine,[88] and, conversely, with the administration of co-agonists, such as glycine, which relieves the symptoms of schizophrenia.[86,88,89] This theory, generally known as the "NMDA receptor hypofunction hypothesis," supports the idea that neurodegeneration due to neuron death is caused by excess release of glutamate and overstimulation of NMDA receptors, known as excitotoxicity.[90] The high influx of sodium and calcium through the glutamate-dependent NMDA channels causes overproduction of free radicals, causing oxidative stress and neuron death.[91-93]

The NMDA receptor hypothesis and the dopamine theory are closely linked, as it has been observed that the NMDA receptors may be responsible for a state of excess dopamine production, and inversely, the administration of dopaminergic antagonists appears to influence the function of NMDA receptors.[94]

Furthermore, the GABAergic hypothesis suggests that an alteration in this transmission system would lead to a reduction in the inhibitor control exerted by GABA on the dopaminergic channels.[95] The Lewis Group at the University of Pittsburgh, pioneers in this field of study, has observed that the pyramidal cells of the cortex and the so-called *candelabra* or adjacent GABAergic interneuron cells are more vulnerable to neuron death in schizophrenia.[95] These neurons are characteristic of the prefrontal cortex and the bodies are smaller and there are fewer dendritic spines in schizophrenia than in healthy individuals. It is suspected that the pruning or synapsis elimination process in patients with schizophrenia does not discriminate and eliminate both weak and strong synapses,[96] or that synapses in schizophrenia are not robust enough to withstand the neuron pruning process.[97] On the other hand, there seems to be a reduction in GABAergic neurotransmission between candelabra neurons and the pyramidal neurons that would affect neuron development and the efficacy connections, as these are weaker and therefore more vulnerable to neuron pruning.[95]

In addition to alterations in chemical neurotransmission, there are markers for apoptosis (or genetically programmed cell death) that seem to be higher in schizophrenia. These markers show that apoptotic hyperfunction may also support the degenerative process in schizophrenia.[98] The cells that are not sufficiently exposed to trophic factors, or those still under the effect of serotonin or glutamate, start the steps leading to cell death by apoptosis through the activation of a chain reaction of proteins such as Ccl2-Bax-Caspase.[37] A high level of Bax/Bcl-2 is indicative of greater vulnerability to apoptosis and patients with chronic schizophrenia show a Bax/Bcl-2 quotient 50% greater than the non-psychiatric population.[67] This may lead patients with schizophrenia to have a greater likelihood of suffering neuron death.

Treatment with antipsychotics

Although there is a wide range of studies on the possible antipsychotic effect on the course of schizophrenia, it is true that no broadly accepted consensus has been reached that supports either hypothesis on schizophrenia.

Some authors have suggested that pharmacological treatment suppresses the symptoms of the illness, but it does not alter the course of the condition or its potential for progression.[71,99,100] However, some studies seem to indicate that antipsychotic drugs may act as neuroprotectors for the nervous system,[78,101-104] preventing[105] or even improving the course of the illness.[106] For example, Bartzokis et al.[78] conclude that on the long term, risperidone injections may prevent the characteristic loss of white matter in the brain in schizophrenic patients. Other studies have observed that if there are long periods of active psychosis prior to initial treatment, the subsequent evolution of the patient is worse, and therefore early pharmacological treatment is advisable in order to improve prognosis.[107,108] Some studies have also shown that the gradual loss of frontal density seen in patients with schizophrenia seems to worsen with the number of psychotic episodes suffered and that, with atypical anti-psychotic medication these changes can be reduced.[109] Indeed, some studies maintain that patients who respond well to treatment present fewer negative symptoms and improved cognitive performance.[78,104]

Recent studies on short and long term treatment for schizophrenia completed by Harrey state that patients who interrupt treatment suffer more relapses than those who continue with medication. This reveals the stabilizing effect of medication on the course of the condition.[110] However, the authors highlight the emblematic situation that in spite of the importance of maintaining treatment, in the long term this can result in a biological readjustment and a drop in efficacy, eventually rendering treatment ineffective or even damaging. In other words, the body becomes accustomed to medication and makes becomes more susceptible to relapses when treatment is interrupted.[111] The authors spent two years following-up patients through their first episodes without pharmacological treatment, and patients with chronic schizophrenia, which revealed that the optimum symptomatic improvement occurs within the first 6 months of treatment and that the progression of the condition may reduce the efficacy of treatment, both initial episode and in patient with chronic schizophrenia.[112]

When taking a closer look at conflicting pharmacological results, it is worth commenting that several experimental studies in non-human subjects have shown neutral, neurotoxic and neurodegenerative effects of antipsychotic drugs on the brain.[113-119] As regards studies with patients, the recent meta-analysis completed by Fusar-Poli et al. analyzed different longitudinal studies on FMR, concluding that the progressive loss of gray matter that characterizes patient with schizophrenia worsens in those who have undergone long term anti-psychotic treatment.[120] However, some studies affirm that treatment has no effect on brain volume.[99]

DISCUSSION

Criticism of the adoption of one of the hypotheses

Different areas of research have made great efforts to shed some light on the etiology and course of schizophrenia. However, as yet there is no theory or hypothesis encompassing all the data in a satisfactory way. In order to be able to conceive the condition as a developmental disorder, clear evidence of untreatable, static early onset must be found. On the other hand, the evidence that would demonstrate schizophrenia as a neurodegenerative disorder would lie in histopathalogical data of neuron degeneration and progressive cognitive deterioration.[39] However, as we have discussed, the majority of the factors studied may be explained by the theory of development or by the hypothesis of degeneration. Depending on the chosen viewpoint, data can be explained in a more or less satisfactory way. For example, when schizophrenia is seen as a developmental disorder, the factors relating to genetics, prenatal and perinatal alterations, environmental factors, etc. are appropriately understood. Meanwhile, evidence of structural, chemical and brain connectivity alterations are better explained through the degenerative theory. Nevertheless, the results of some studies are questionable and do not clearly support one theory or the other, as is true for example in the case of studies on anti-psychotic treatment and cognitive function.

It is very difficult for the large amount of evidence available on schizophrenia to be satisfactorily explained via a single, rigid and firm model, based merely on the theory of neurodevelopment or neurodegeneration. Skepticism when proposing alternative models to explain the illness and the shortage of proposals integrating both models may result in a lack of regard for the main scientific purpose, which is ultimately to find an explanation for the evidence and therefore understand the truth.

Bearing in mind that the presence of an alteration in neurodevelopment does not exclude the possibility of a simultaneous neurodegenerative process and vice versa, the neurodegeneration theories may explain many characteristics of the course of the condition and later onset, while the hypothesis of neurodevelopment provides a good explanation for factors relating to origin and early stages.[6] This reflection has given rise in recent times to consideration the pathogenesis of schizophrenia as a *progressive neurodevelopment disorder.*[39,121,122]

Integrating model: progressive neurodevelopment disorder

Based on the studies reviewed, in this section we venture to suggest an alternative model that defines schizophrenia

as a condition in which development is altered and that progresses consistently and variably. By definition it is a condition that evolves throughout life. However, it would not be categorized by continuing progression, in the sense of a primary neurodegenerative process, but would progress transitorily in stages,[79] creating patient subgroups depending on how their condition evolves. There would, therefore, be patients who improve, others who worsen and others who remain stable.[110] In general, the early stages of the condition are not distinguishable from normal healthy development and the late stages of the condition are similar to degenerative illnesses in which capacities are severely affected compared with control subjects.[54] In this model, schizophrenia would not be a neurodegenerative condition in the traditional sense, which would not suggest it is a purely neurodevelopment condition.[123] This theory would therefore accept the following premises in the study of schizophrenia: 1) that it starts prenatally; 2) that it progresses until reaching a critical threshold; 3) that it causes a gradual loss of brain mass that slows over the years and 4) that it causes cognitive and function deterioration.[122]

Future studies

Further efforts should focus on understanding the course of this condition. Relatively little attention has been paid to neurodegenerative processes, despite the clinical evolution of the condition and the fact that in the clinical context, most patients experience different levels of cognitive and behavioral deterioration.[46] This is due to the traditionally held belief of neurodegeneration. It is nevertheless possible that the true course of the disease is obscured by several factors such as methodological, histological and imaginary complications, and by the absence of standardized tests for evaluation, simple heterogeneity (acute, chronic, stable, etc.) the potential effects of treatment, etc. In addition to this, there is an insufficient longitudinal follow-up of current studies.[54] Just as the onset of the condition is affected by genetic and environmental factors, so is its evolution, and this is something that should be elucidated in order to ensure the success of future intervention and prevention, and to better understand the etiopathogenesis of the condition.[124]

CONCLUSION

We have seen how the factors involved in the etiopathogenesis of the condition are multiple, and it is complicated to integrate them given that some of the findings are inconclusive, replicable, or may even at times be contradictory. It may be that this multiplicity of variable and results underlie an equally multiple etiopatogenesis for schizophrenia, that can only be deciphered through the integration of several hypotheses. We must maintain a broad perspective regarding possible explanations for the condition that does not lead us to bias the information and that helps to reinforce new and future studies for deciphering the origin and course of this complex web of symptoms, where depending on certain variables as yet unexplained, we can establish subgroups of patients with schizophrenia using different development patterns or "trajectories" of evolution.

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