INTERDISCIPLINARY FACTORS OF NEUROPATHOLOGY IN SCHIZOPHRENIA

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In the etymology of schizophrenia, the genetic component seems to play an essential role. Studies have shown more than 130 genes of susceptibility for schizophrenia: the majority of these studies, however, has yet to be confirmed- they are searching for more definition on the relevant functions of the genetic variation of schizophrenia. Recent studies suggest that a cluster of candidate genes in the interconnected network pathways are implicated in transmission of the glutamate the plasticity of the synapses, in oxidative stress, myelination and the profitability of oligodendrocytes. Previous neuropathological studies on schizophrenia did not identify specific neurodegenerative characteristics of this disease. Scientific evidence suggests that the physiopathology of schizophrenia involves alterations of the intracellular transmission pathway, those which are associated with reduced cerebral volume in some structures of white and gray matter. In particular, in schizophrenia, a reduction of medium cerebral volume has been observed, as has a reduction of the cortical regional volumes with reference to the frontal, temporal, and parietal areas of the brain - this is all in addition to a reduction of the prefrontal cortex, hippocampus, amygdala, thalamus, and the cerebellum. The cytoarchitectonic alterations in schizophrenia may be an expression of the pathology's processing, as are axonal damage and loss, reduction of myelination, and loss of neuropil. These all contribute to the reduction of the volume of the cerebral parenchima, and the corresponding augmentation of the cerebral spinal fluid. The inheritance of schizophrenia may appear high/elevated, but not a certain eventuality. In analysis of subtype specifics. However, this statistics remains significant in all studies. The role of the environmental factors in the development of schizophrenia is highlighted by studies which have been conducted on monozygotic patients affected by schizophrenia. While their genetic code is 100% similar, that is to say, entirely identical, one of the pair can be diagnosed as schizophrenic, while the other of the monozygotic pair has the 50% of the possibility not to contract schizophrenia. It is well known that genetic and environmental factors influence multiple aspects of human behavior, they can increase the susceptibility towards a mental disturbance. The reciprocal effects of these factors are placed in two distinct and diverse categories: gene environment interaction, which expresses the terminal genetic variations of susceptibility to environmental risk, and environmental gene correlations, where the genetic variability can increase or reduce the likelihood of the exposure to environmental determinant risk, includes early stressful events of life.

Schizophrenia is a debilitating psychiatric disorder that affects 1% of the worldwide population. It occurs as a sporadic and as a heritable disease, typically presenting in adolescence or early adulthood, and leads to great disability and distress. Characteristics include positive symptoms (delusions,

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hallucinations, and disorganized thought, speech and/or behavior), negative symptoms (amotivation, social withdrawal, poor relatedness and a reduction in affective expression) and cognitive deficits (poor working memory and deficits in attention, processing speed and executive function) (1).

Genetic Components

In the etymology of schizophrenia, the genetic component seems to play an essential role: the risk of devloping disease in the family of the patients that are affected by schizophrenia is 5-10 times higher, compared to the general population. This risk is gradually reduced with the distance of degree of relation to the affected family member (2). The study of twins has shown more likelihood of a concordance for monozygotic twins (about 45%) compared to dizygotic twins (about 15-20%). This is in accordance with the interrelationship of the common genes which the twins share (3).

Until now, linkage and association studies have shown more than 130 genes of susceptibility for schizophrenia (4): the majority of these studies, however, has yet to be confirmed - they are searching for more definition on the relevant functions of the genetic variation of schizophrenia (5).

Recent studies suggest that a cluster of candidate genes in the interconnected network pathways are implicated; transmission of glutamate, plasticity of the synapses, oxidative stress, myelination and the profitability of oligodendrocytes (5-7).

Cyto-architectonic alterations

Previous neuropathological studies on schizophrenia did not identify specific neurodegenerative characteristics of this disease (8). Scientific evidence suggests that the physiopathology of schizophrenia involves alterations of the intracellular transmission pathway, those which are associated with reduced cerebral volume in some structures of white and gray matter (9-12).

For purpose, postmortem and brain-imaging studies have shown and proved the existence of a reduction of dendritic arborization and cerebral density in schizophrenia (13). This provokes the hypothesis of a deficit at the level of cerebral connectivity in the physiology of this pathology. This type of abnormality may be quantified using Magnetic Resonance Imaging (MRI) associated with specific software analysis. In particular, in schizophrenia, a reduction of medium cerebral volume has been observed, as has a reduction of the cortical regional volumes with reference to the frontal, temporal, and parietal areas of the brain - this is all in addition to a reduction of the prefrontal cortex, hippocampus, amygdala, thalamus, and the cerebellum (14-19). To date, diverse meta-analysis and revisions have been conducted on the cerebral alterations associated with schizophrenia, and of these relevant neuromorphology alterations, the augmentation of cerebral ventricular volume, expressed in terms of ventricular brain ratio, (VBR), is certainly the more frequented of the data that is available (20-21). In a more profound meta-analysis on the study of the regional cerebral volumes in schizophrenia, Wright and et al. have found that in 58 studies involving over 1,588 patients, all of whom were affected by schizophrenia, the average cerebral volume in its entirety of the patients was shown to be 2% less than that of the average cerebral volume of healthy subjects who were used as controls (12). Another meta-analysis with more strict inclusion criteria has shown that the superior temporal gyrus and the Sylvian fissure are biased towards the asymmetrical left side and that they are significantly less pronounced in patients with schizophrenia in comparison to healthy subjects (16). Other meta-analysis have been concentrated on more localized metamorphic abnormalities.

For example, Zakzanis et al. have reviewed the consistency of the results of papers published on schizophrenia between 1980 and 2000, and their research showed an abnormality in the temporal lobes of patients with schizophrenia. Their findings were in agreement with previous studies which had proved abnormalities in the structure and in the function of the same areas (16). Other meta-analysis have been concentrated on the medial-temporal and diencephalic structures, finding several diverse deficits in this gray matter area (22-23).

Neurotrophic alterations

The cytoarchitectonic alterations in schizophrenia may be an expression of the pathology processing, as are axonal damage and loss, reduction of myelination, and loss of neuropil. These things all contribute

to the reduction of the volume of the cerebral parenchima, and the corresponding augmentation of the cerebral spinal fluid. Based on the hypothesis of Selemon on the subject of reduction of the neuropil, which is the inter-neural space in which occurs the synaptic processes, and which also contains the axonal termination, and Dendritic astrocytes. This explains the cerebral volume loss in the neocortex of the subjects affected by schizophrenia (24). The reduction of the cerebral volume which is found in schizophrenic patients is probably due to a reduction in both the synapses and also the inter-neural space. According to Selmon, this is the consequence of an augmentation of cellular density, and not the consequence of a reduction of the total number of neurons (25-26).

Even though the study in this field has not yet been successful in reporting a constant on any singular region in order to identity it as abnormal, it seems important to underline as some studies on twins and brothers have demonstrated inheritance of the structural modification of the brain, as previously discussed. These studies suggest the possibility of genetic mediation of these alterations and show them as potential endo-phenotype of this particular disease

Environmental components

The inheritance of schizophrenia may appear high/elevated, but not a certain eventuality. This inheritance factor comes in at about 80% and the tendency is to diminish with using the most restrictive diagnostic criteria in analysis of subtype specifics. However, this statistic remains significant in all studies (27). The role of the environmental factors in the development of schizophrenia is highlighted by studies which have been conducted on monozygotic patients affected by schizophrenia. While their genetic code is 100% similar, that is to say, entirely identical, one of the pair can be diagnosed as schizophrenic, while the other of the monozygotic pair has the possibility of not being schizophrenic (3). It is well-known that genetic and environmental factors influence multiple aspects of human behavior - they can increase the susceptibility of an individual to mental disturbance. The reciprocal effects of these factors are placed in two distinct and diverse categories: gene environment interaction, which expresses the terminal genetic variations of susceptibility to environmental risk; and environmental gene correlations, where the genetic variability can increase or reduce the likelihood of exposure to environmental determinant

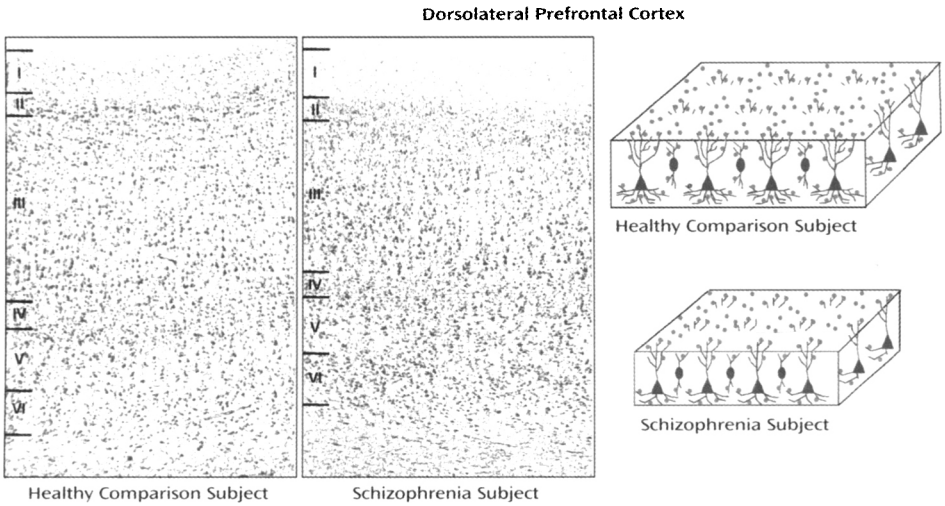

Fig. 1. *Cerebral tissue microscopic analysis, which shows an augmentation of neural density in the prefrontal cortex, Brodmann 9 area, III-IV and 46, stratifications II-IV and VI respectively of 17%, 21%, in the brains associated to the schizophrenic subjects (Selemon, 2004).*

risk (28), including early stressful events of life (29). Because of the difficulty in translating the complex psychological phenomenon in measurable and objective variables, the research is focused on specific factors. Among these are the complications of pre- and post-natal viral infections, substance abuses, and stressful events, which are best described as quantitative variables, the effect of which on the development of schizophrenia is facilitated by genetic component (30). It is probable that the individuals at-risk for schizophrenia have varying degrees of reactivity to environmental factors (some subjects are more sensitive to some factors, and some are less sensitive than others). These diverse grades of reaction may be genetically determined (31). Studies conducted on the highest-risk individuals (those with the highest risk morbidity between individuals genetically predisposed towards the development of schizophrenia) offer many more cases in which the exposure to the known factors of environmental susceptibility cannot be translated in an augmentation of the case of schizophrenia, in the sense that it cannot be blamed for the growth of a schizophrenic case (32-33). This fact has induced geneticists to consider schizophrenia in the same manner as other conditions, other "complex disorders". One complex disorder from the genetic perspective is:1) a disorder that occurs less frequently in the general population; 2) one which does not follow the Mendelian laws of heredity; 3) the pathogenesis implicates the interaction complex of more than one altered gene with more than one environmental pathogenic factor, including the stressful events of early life (34, 29).

Interdisciplinary research

With the term of Interdisciplinary research, we intend the involvement and collaboration of more disciplines for the analysis of a phenomenon. This method is adapted principally for the study of the phenomenon and complex systems, with a multi-dimensional and global approach. This method may promote the comprehension of the individual. It is also intended to promote a biological, psychological and social complicity in which the subjectivity of neurobiology and environment are equally considered.

The concept of endophenotypes is like a bridge, in the sense that it links the inter-disciplinary studies in the research of schizophrenia. The meaning of the term endophenotype is "downstream" of the clinical phenotypes, not visible to the assisted human eye, as cytoarchitetonic alterations and neurotrophic alterations. It is only visible with neuropsychology tests, or with neurophysiology techniques, as Magnetic Resonance Imaging, which are present in affected patients who have psychiatric disturbances and which can also be seen in their relatives. They contribute risk factors for the development of the disease, because they are directly determined by the genotype.

The concept of endophenotype was adapted for filling the gap between available descriptors and between the gene and the elusive disease processes. The identification of endophenotypes, which do not depend on what is obvious to the unaided eye, can help to resolve questions about etiological models. Endophenotypes provide a means for identifying the "downstream" traits or facets of clinical phenotypes, as well as the "upstream" consequences of genes and, in principle, could assist in the identification of aberrant genes in the hypothesized polygenic systems conferring vulnerabilities to disorders (36).

There is growing recognition that schizophrenia is caused by numerous genetic and environmental factors, each of which have individually small effects and which only result in overt disease expression if their combined effects cross a hypothetical "threshold of liability." Such complexity poses considerable challenges to traditional genetic linkage strategies, which are most effective in the context of diseases or traits influenced by a single major gene. The use of endophenotypes, intermediate phenotypes that form the causal links between genes and overt expression of disorders, promises to facilitate discovery of the genetic and environmental architecture of common mental disorders and thereby suggest novel strategies for intervention and prevention based on an understanding of the molecular mechanisms underlying disease risk and manifestation. The genes influencing liability to schizophrenia are likely to impinge on multiple neural systems known to be impacted in these illnesses, including cortical and subcortical dopaminergic, serotonergic, and glutamatergic systems that mediate a number of neurocognitive and affective processes, such as attention, learning, memory, language, stress

sensitivity, emotional regulation, and social cognition (37-38).

It will be necessary to find a possible endophenotype to reduce the gap in understanding between the schizophrenic process and the genome and manifestation of this pathological disease. The multi-dimensional research in schizophrenia appears essential, in that the purpose of it is to ameliorate the knowledge of the mechanism on which are based the psychiatric disturbances of schizophrenia. In the search for potential endophenotypes, what will become more significant is the new neurobiological diagnostic criteria that goes beyond symptomatic diagnosis.

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