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Journal of Brain and Neurological Disorders
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Review Article

# Discordance of brain viral infection in one monozygotic twin from a schizophrenic mother and grandmother. Prenatal study

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**Received Date:** January 03, 2025 | **Accepted Date:** January 10, 2025 | **Published Date:** January 20, 2025

**Citation:** Segundo Mesa, (2025), Discordance of brain viral infection in one monozygotic twin from a schizophrenic mother and grandmother. Prenatal study, *J. Brain and Neurological Disorders*, 8(1): **DOI:10.31579/2642-973X/132**



## Abstract

Schizophrenic monozygotic twin's concordance is of only 45% although both twins share 100% of the derived genoma of a single zygote for what the discordance in monozygotic twins is related to the influence of prenatal environmental factors independently of genetic factors. These prenatal environmental factors are related to the alterations in the brain and the skin more frequently observed in patients since both tissues are derived from the embryonic ectoderm. This fact explains the anomalies of the nervous system together with anomalies of the hair, face, hands and feet more frequently observed in schizophrenics discordant twin than in the normal population. Among the environmental factors virus occupies a more and more excellent position for the results obtained in clinical observations in human and in experimental animals. A virus acting in this first phase of development, especially during the 2do. pregnancy trimester can explain the anomalies observed in both structures derived of the embryonic ectoderm in the affected twin. In the present work are exposed the results obtained in an ultrastructural study in samples of the brain of two monozygotic twin fetuses with strong antecedents of schizophrenia in their family. The obtained findings indicate an infection for the virus herpes simplex hominis type I [HSV1] in the brain of one of the twins and mitochondria alterations. The obtained results can explain the discordance of the illness found in the postnatal clinical and epidemiologic studies. It should be considered their relation to the viral etiology to be the first direct evidence of virus in the brain of a fetus from a schizophrenic mother with important biological load of family schizophrenia.

**Key Words:** schizophrenia; fetus; discordant monozygotic twins; virus; electron microscopy; amniotic fluid cells; mitochondria

## Introduction

There are two facet of development that may be implicated in the pathogenesis of schizophrenia: a) the occurrence of non-specific factors, presumably genetic (developmental instability), and b) any damage experienced for the period of development. The insults that are associated to critical periods of brain development are likely to be associated with the development of schizophrenia. The fact that genetically identical twins can be discordant for schizophrenia suggests a non-genetic mechanism or a mechanism involving an interaction of genotype and environment. Differential exposure to such early risk factors may contribute to twin discordance for psychotic disorder. The hypothesis that viruses cause schizophrenia and other neurological disorders was proposed in the 19th century and it is still accepted as one of the most common associations [1]. In many studies, influenza infection and fever, particularly during the second trimester, have been implicated as factors in the development of the condition [2,3]. However, recent studies have shown no evidence of direct invasion of the foetus by the influenza virus [4]. PCR experiment found no evidence for mRNA for three H1N1 viral genes in the placenta or in the brains of exposed offspring. In nearly all studies of prenatal influenza and schizophrenia, the presence of the exposure was based solely on whether an individual was in gestation at the time of an influenza epidemic, with no confirmation of maternal influenza infection during pregnancy.

Direct viral invasion of the embryo or foetus appears unlikely to be the cause. Although serological evidence of influenza infection has been found in mothers of offspring affected with schizophrenia "there was no microbiological or histopathological evidence that the virus had infected the foetus in these cases" [5]. Presumptive evidence for a viral aetiology of schizophrenia requires the demonstration of a virus, antigen or viral antibody. In previous works we have obtained results that constitute direct evidence in two of three of these requirements, virus and antigen: a) in post-mortem studies of the brain of young schizophrenic adults, b) in animals experimentally inoculated with cerebrospinal fluid from schizophrenic patients and c) in the temporal lobe of foetuses from schizophrenic mothers. Until our report, evidence supporting the concept of virus-cell interaction in the neurodevelopmental hypothesis of schizophrenia had been indirect. Virus particles had never been demonstrated. In our studies of foetuses from schizophrenic mothers we have also observed mitochondrial structural anomalies. In the last years mitochondria have been objects of study in schizophrenia by several researches. There is increasing interest in the possibility that defects in the

mitochondrial genome may play an important role in psychiatric illness. The study in mitochondrial DNA [mtDNA] of common polymorphisms, somatic mutations, and rare mutations in larger populations may lead to a better understanding of the pathophysiology of psychiatric disorders [6,7]. Viruses can localize in mitochondria and disrupt their integrity. Therefore, their action, in cooperation with other cellular products, already viral or induced, is able to commit the functionality of the mitochondrial membranes of the infected cells. The present paper is related to our electron microscopic findings in the temporal lobe of foetuses from schizophrenic mothers, some of them with strong familial antecedents of schizophrenia. We have considered the hypothesis that the brains of fetuses from schizophrenic mothers would have alterations at cellular level that would allow to differing them of healthy controls.

### Subjects

Previous informed consent written by the relatives or legal representatives and the patients, when their clinical condition allowed them to make it and with the approval of the Committee of Ethics of the Institution, a brain sample 16 weeks gestational age was obtained corresponding from the tip of the left temporal lobe of five foetuses from schizophrenic mothers [DSM-IV diagnostic criteria] whose pregnancy was interrupted for medical indications and three foetuses of mothers without antecedents of psychiatric or neurological illness. The diagnosis in the schizophrenic mothers was: hebephrenic schizophrenia, 1 case, paranoid schizophrenia, 3 cases. In one of the paranoid schizophrenic mothers the samples were obtained from two aborted foetuses [monozygotic, monochorionic and biamniotic twins]. One of the twins presented cryptorchidism. The other samples were obtained from one hebephrenic schizophrenic mother and two paranoid schizophrenic mothers. In the cases of schizophrenic mother's, it was verified strong family antecedents of the illness.

### Staining process

The obtained samples were fixed in glutaraldehide-paraformaldehide 1% for 1 hour proceeded later on to the blockade of the endogenous peroxide with methanol and hydrogen peroxide during thirty minutes to ambient temperature and washed with several volumes of PBS and TRIS. Normal goat serum was used diluted at the 1:5. It was added the rabbit antiserum anti-herpes simplex hominis type I [HSV1, DAKO LAB.] during 24 hours and washing with TRIS. Diaminobenzidine [DAB] was used to ambient temperature and washed with TRIS. Post-fixation was carried out with osmium tetroxide and washed with buffer phosphate. Ethanol, absolute ethanol, and propylene oxide were applied: being proceeded to the inclusion in Epon I during sixty minutes, Epon II during the whole night. The definitive inclusion was made for blocks with dilutions from the antiserum to 1/10 and 1/20 with blocks controls of each dilution. The samples were observed in a Tesla BS 500, Hitachi 9500 and Philips 300 Transmission Electron Microscopes.

## Results

In one of the monozygotic twins studied fetuses [the one that presented cryptorchidism] it was observed within the nucleus of neurons the presence of incomplete viral particles of 100 nm occupying the center of an electron lucid area [Fig.1,2A,2B]. The inclusions with particles appeared in number from 2 to 8 for nucleus, with great incidence in their appearance. In the rest of the studied fetuses a smaller number of intranuclear particles were observed with the same characteristics of being surrounded of a clear halo [Fig. 2C, 2D]. The viral particles were not observed in the rest of the cells of the nervous system, neither the immunologic reaction. In the other monozygotic twin fetus, the viral intranuclear particles was not observed [Fig. 2E]. In the inmuno-electromicroscopic study a positive reaction was observed against the virus herpes simplex hominis type I in mature particles in the cytoplasm of the neurons and within the nucleus [Fig.3]. Besides the viral particles mitochondria alterations were observed in the affected twin, being observed an increased number of large mitochondria in the cytoplasm of the neurons corresponding to the granular layer of the temporal cortex [Fig. 4]. The general appearance of the affected mitochondria showed loss of the internal membranes that presented as empty mitochondria. These structural anomalies were observed only in the foetuse's from schizophrenic mothers. None signs or clinical symptoms of infection were observed in the schizophrenic mothers.

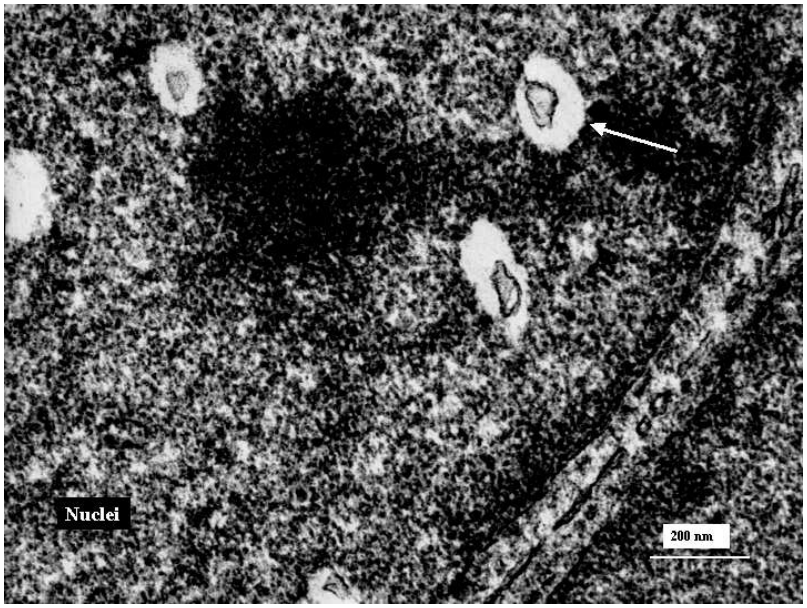
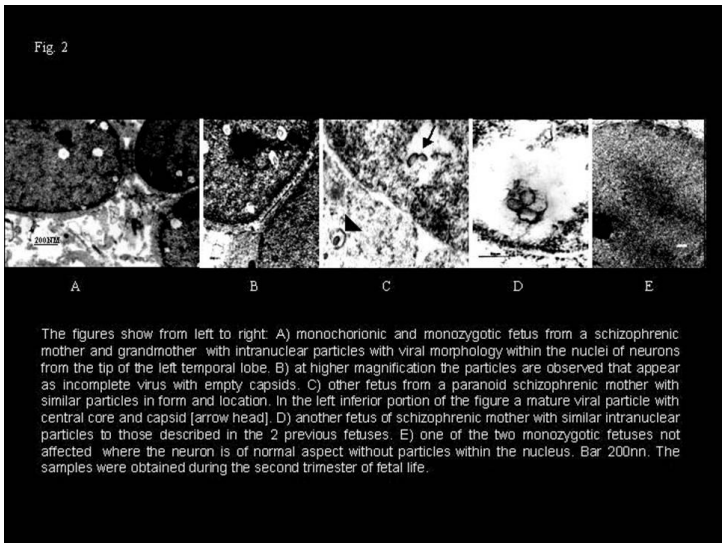



**Figure 1:** Incomplete viral particle's [white arrow] within the nucleus of a neuron of a monozygotic twin foetu's from a paranoid schizophrenic mother and grandmother.



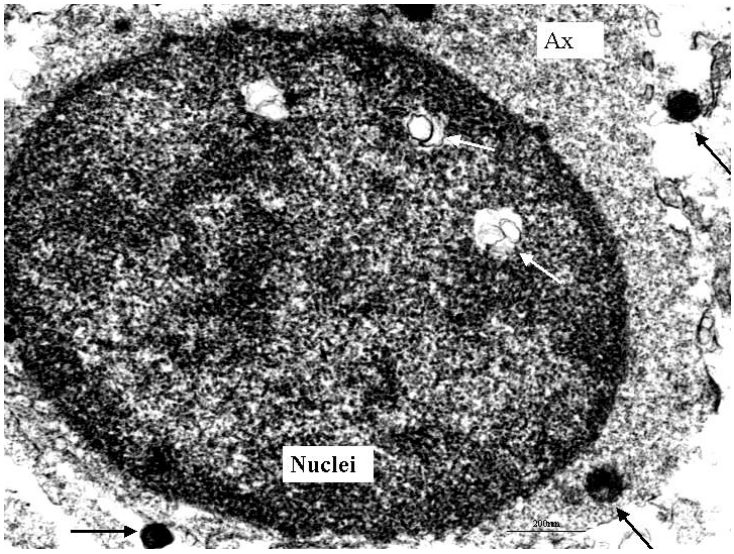




**Figure 3**: Intranuclear incomplete viral particles [white arrows] and intracytoplasmic complete viral particles labelled with anti-herpes simplex hominis type I virus immuno-peroxidase antisera [black arrows]. Ax= axon. Monozygotic fetus.

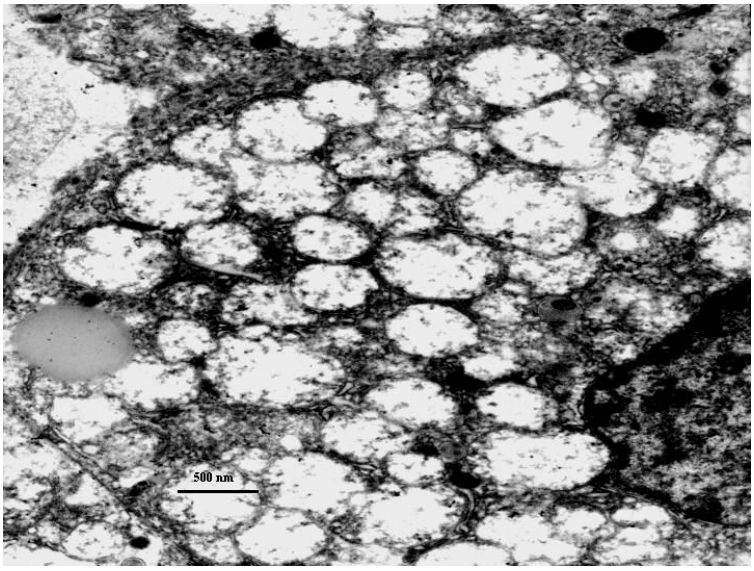



**Figure 4**: Granular neuron with the cytoplasm completely filled with large mitochondria. Most of the mitochondria are empty of crests.

## Discussion

Schizophrenia has been considered a neurodevelopment disorder that is associated with a variety of prenatal environmental insults on the brain that include infections [8-10]. Although the infectious agents have been proposed as one of the factors of prenatal risk for schizophrenia there are no evidence of the association of a specific infectious agent and cerebral damage in that stage of neurodevelopment [11,12]. In addition to this fact, it is not clear when the prenatal abnormalities are originated in patient with schizophrenia although the biggest quantity of data guides toward the second pregnancy trimester. The knowledge of that moment in the appearance of the structural abnormalities would allow us a better identification of the processes of neurodevelopment that contribute to the risk of suffering schizophrenia. In the last decades it has been observed in the medical literature an increment in the interest in prenatal studies related with the etiology of schizophrenia [13-24], especially in subjects on high risk of suffering the illness [25-28] and are included in this study the offsprings of schizophrenic mothers to be observed in them a bigger probability to suffering schizophrenia [29,30].

**Hypothesis:** As mentioned above we have considered the hypothesis that the brains of fetuses from schizophrenic mothers would have alterations at cellular level that would allow to differing them of healthy controls. Unfortunately, the human brain is not exposed to a direct observation in that stage of the life. Only an eventual circumstance as it is the interruption of a pregnancy for medical reasons that would allow us to observe possible alterations at cellular level. The magnitude of the obtained results depends on the resolution of the technique that is used.

**Electron microscopic studies:** The only direct studies of the brain of fetuses from schizophrenic mothers with electron microscopic techniques carried out in the world up to where we know were carried out by us. In our studies of electron microscopy of the brain of fetuses from schizophrenic mothers whose pregnancies were interrupted for medical reasons we had the opportunity to observe at cellular level the possible alterations that we had outlined in hypothetical form that included a possible viral infection [31,32]. Our observation of viral particles within the nucleus of neurons, identified by inmuno-electromicroscopy related to the herpes simplex hominis type 1 virus, is the first direct evidence of this virus in the brain of fetuses from schizophrenic mothers and relates this result with the etiology of the illness [33,34]. The discovery in the temporal lobe that is the region of the nervous system affected by this virus in clinical observations constitutes the region of the brain affected in schizophrenia in turn. Postnatal studies with other investigation designs confirm the relationship of this virus with the temporal lobe and with the illness [35-37].

We have seen herpes virus particles and herpes virus antigen in three experiences: foetuses of schizophrenic mothers [38,39], adult schizophrenics and animals inoculated with CSF from schizophrenic patients. A viral hypothesis can coexist with the clear evidence for genetic factors in schizophrenia since viruses can integrate into the genome and be transmitted to offspring as genetic material or could interact with cells in events occurring prenatally. Viruses like herpes simplex may remain latent and transmitted from generation to generation in a pattern that would make it appear to be a genetic disease. The concept of latent viral infections with periodic reactivation is now well established. The property of latency of the herpes virus in relation to other viruses [influenza, retrovirus] and their reactivation for factors of different nature could explain the appearance of the symptoms in later stages after an initial aggression in the intra-uterine stage [40,41]. The presence of virus particles in the brain of studied fetuses from schizophrenic mothers favors the possibility of virus insult to the brain at crucial times in the growth and differentiation of areas of limbic regions.

### Twin studies:

An important aspect to be considered in our studies is that related with twins [see family history]. Only one of the twins presented viral infection and mitochondria alterations. An element in favor of prenatal environmental factors in the etiology of the illness is the one derived of epidemiological studies that indicate that only 45% of both twins suffer the illness in spite of sharing a single genome. A case is described of monozygotic twins discordant for schizophrenia that illustrates possible causal events of prenatal underdevelopment, morphological changes in the brain, poor premorbid functioning, and the development of schizophrenia. “The affected twin was born with a birth weight of 1620 g, whereas the unaffected twin weighed 2300 g at birth. Marked differences in sociability and intelligence were observed between the twins from early childhood. Magnetic resonance imaging of the brain revealed high-intensity signals in the white matter and enlarged ventricles in the affected twin, while no such abnormality was detected in the well twin” [42].

In our studies the affected twin had crypthorchidia. Cryptorchidism is a disease state with a spectrum of associated findings rather than an isolated malformation [43] and that malformation could be also in our study the result of the active viral infection observed in the neurons. The grey matter decrease in schizophrenic patient has been observed in the so-called regions of interest [ROIs] and has been correlated to functional disturbances. In a functional magnetic resonance imaging twin study was observed that the affected twin displayed relative bilateral decrease in N-acetylaspartate/creatin concentration in the anterior hippocampus compared with the healthy one. The authors concluded that this is evidence for non-genetic impairment of cerebral lateralization in monozygotic twin with schizophrenia [44].

In other studies, the brains of 15 monozygotic and 14 same-sex dizygotic twins discordant for schizophrenia (patients) and 29 healthy twin’s pair-wise matched for zygosity, sex, age, and birth order were studied using high-resolution magnetic resonance imaging scans. Intracranial and whole-brain corrected frontal lobe volumes were smaller (4.6% and 2.7%, respectively) in discordant monozygotic twins as compared with healthy monozygotic twins. Irrespective of zygosity, discordant twins had smaller whole-brain (2%), parahippocampal (9%), and hippocampal (8%) volumes than healthy twins. Moreover, patients had smaller whole-brain volumes (2. 2%) than their no schizophrenic co twins, which in turn had smaller brains (1%) than healthy twins. Lateral and third-ventricle volumes were increased in discordant dizygotic twins as compared with healthy dizygotic twins (60.6% and 56.6%, respectively). Finally, within discordant twins, lateral ventricles were larger (14.4%) in patients than in their no schizophrenic co twins. The authors concluded that “smaller intracranial volumes in the monozygotic patients and their co twins suggest that increased genetic risk to develop schizophrenia is related to reduce brain growth early in life. The additional reduction in whole-brain volume found in the patients suggests that the manifestation of the disorder is related to (neurodegenerative) processes that are most likely no genetic in origin” [45]. However, in our opinion the possibility that both twins have been affected in different degree by a common aggressor agent [virus] it should be kept in mind. Other studies have found variation in hippocampal and ventricular volumes within discordant monozygotic pairs and relate these findings to inheritance [46].

However in our opinion it should be considered the possibility that the environmental factors [virus] exercised a bigger impact in the brain during the intra-uterine stage of those twins that later on suffer the illness and it is in agreement with the results obtained by others authors who consider that the quantitative results of diminished hemisphere volume and length in the twins with schizophrenia suggest that this is a bilateral phenomenon that may be dependent, at least in part, on environmental factors [47-49]. In studies of twins discordant for schizophrenia have been observed that the twins discordant for schizophrenia had significantly greater absolute intrapair differences in total finger ridge count and significantly greater percent intrapair differences than the normal twins; i.e., their fingerprints were significantly less "twin-like." This study suggested that various second-trimester prenatal disturbances in the epigenesis of one twin in a

pair discordant for schizophrenia may be related to the fact that only one of the twins expresses his or her genetic predisposition toward schizophrenia.

They expressed that it is consistent with a “two-strike" etiology of schizophrenia: a genetic diathesis plus a second-trimester environmental stressor [50]. In other works, dermatoglyphic markers of prenatal growth were obtained by established procedures from 26 monozygotic twin pairs discordant for schizophrenia, 13 monozygotic twin pairs concordant for schizophrenia, and several normal monozygotic twin samples. The a-b ridge count differences between the affected and well co-twins were greater than those found for concordant and normal monozygotic pairs. In comparison with their well co-twins, the affected twins, in discordant pairs, had developed fewer epidermal ridges in the a-b interdigital area of their right palms. In contrast, no significant differences were found between the affected twins and their well co-twins on markers associated with foetal development before 13 or after 15 weeks estimated gestational age. The authors arrived to the following conclusion: “Because the a-b ridges are known to complete development between 13 and 15 weeks estimated gestational age, the results provide physical evidence suggesting that the schizophrenia-affected monozygotic twins alone experienced a time-specific and time-limited dysgenesis during this time” [51]. As mentioned only 45- 50% of monozygotic twins suffers of both the illness that led in 1967 to the hypothesis that the schizophrenia phenotype was an expression of the genotypic vulnerability that interacts with prenatal environmental experiences [52]. Our observations of discordance of viral infection in one of the monozygotic studied fetuses not only favor the prenatal origin of the illness and the viral etiology, but also the discordance of the illness observed near 50% in monozygotic twins [53]. The observation of HSV1 in our immune-electronmicroscopy post-mortem studies in the temporal lobe of the brain in the three experiences already mentioned makes us to consider this virus as the etiological agent since the postulates of Koch have been partially fulfilled [54]. According to Rutten [55]: “Of particular note is the high degree of discordance between monozygotic (MZ) twins for schizophrenia and bipolar disorders. Such phenotypic discordance between MZ twins is often attributed to nonshared environmental factors, although the empirical evidence for such a large environmental contribution to either disorder is still lacking, with no specific environmental risk factors being conclusively linked to etiology. The mechanism through which these environmental factors act upon molecular and cellular biological machineries in the human brain and ultimately give rise to psychosis-related phenotypes and pathology remains poorly understood”.

Our discoveries of HSV1 in the brain of fetuses from schizophrenic mothers can be the answer to this question considering the discordance of viral infection specifically found in the brain of one of the studied monozygotic twins. It is the first direct evidence of viral particles in the central nervous system in fetuses from schizophrenic mothers at ultra-high risk of suffering the illness in the critical period of neurodevelopment. It is the first direct epigenetic evidence of a specific prenatal infection in the neurodevelopmental theory of schizophrenia. It is appropriate with the current interest on the genesis and the epigenesis of schizophrenia in relation to their prenatal origin [56,57]. Unfortunately, we cannot compare these results with similar studies in the medical literature. Electron microscopic studies of fetuses from schizophrenic mothers don't exist as far as we know. It is in fact the lapse of time that mediates between the embryonic development and the post-natal period where it has been considered theoretically that this period of time, especially the second trimester of the fetal development is the critical moment where it could be found elements that could explain the etiology and the physiopathology of the illness. When looking for in -Index Medicus and PubMed- using the key words: schizophrenia, electron microscopy and fetus only appears published our work in spite of the evidences that point out a relationship among the already mentioned second pregnancy trimester [fetal period] and an aggressor agent in the neurodevelopmental theory of schizophrenia.

**Mitochondria findings:** Evidences accumulated in the last decade suggest a role for mitochondrial dysfunction in the pathogenesis of schizophrenia, bipolar disorder and other psychiatric diseases [58]; nevertheless, there are few studies of mitochondria in schizophrenia by electron microscopic techniques. Most studies have used indirect methods to find mitochondrial dysfunction in schizophrenia and bipolar disorders. Among these methods stands out quantification of total mitochondrial DNA and mitochondrial common deletion with contradictory results [59]. Most of these studies were limited to the frontal cortex [60]. In relation to methods of direct analysis there are few publications. The unique electron microscopic studies that offered details on the ultrastructure of the nervous system in schizophrenia began in the 1970s. Especially in the study of embryos of schizophrenic mothers almost all the studies were carried by Russian researches [61,62]. In these studies, they stand out the alterations found in the brain of embryos in different evolution stages from 7 up to 12 weeks. The characteristics of the cellular changes in the brains of embryos of schizophrenic mothers consisted on a bigger development of the membrane system. The mitochondria alterations were very evident with increases in their number, in their size and with destruction of the crests [63,64]. The mitochondria alterations have been interpreted as part of a general process of membrane alterations in schizophrenia [65].

The pathophysiological role of the mitochondria alterations in schizophrenia could be related not only to the cell oxidative process but also in the cell conduction system due to the membrane commitment. Virus can interact with mitochondria. There are several reports in this sense [66-69]. Most of them are related to herpes virus. Particularly herpes simplex virus eliminates host mitochondrial DNA [70].

## Conclusion:

When an infectious agent is observed in an illness of unknown etiology it has been always considered: if the discovered agent is etiologically related or not with the illness in question. Related to our results: lead to the question whether prenatal exposure to the virus observed is a risk factor for suffering schizophrenia later on. We must consider:

1. It can be a viral infection in the patients that affected the fetuses and not related with the etiology of the illness.

2. It can be a viral infection in the fetuses and the patients related with the etiology of the illness. In this sense several favorable circumstances converge: A. Second pregnancy trimester B. Family antecedents of schizophrenia and of severe neurodevelopmental disturbances C. Presence of an incomplete viral form D. Affectation of the neurons and of the nucleus mainly E. Discordance of infection in monozygotic twins F. Ultra-high risk. Familial aggregation of schizophrenia. Mother and grandmother schizophrenics and two schizophrenic’s aunts in twins. Congenital malformations in two uncles. G. None signs or clinical symptoms of infection were observed in the mothers neither in the fetuses H. Not inflammatory reaction in the brain tissue I. Similar previous findings in adult schizophrenics and in experimental animals J. Samples from the tip of the left temporal lobe K. Relationship with the herpes simplex hominis type 1 virus L. Similar findings in other fetuses from schizophrenic mothers not in controls M. Similar findings in the placenta in one study

**Recommendations:** Since the first version of the mild encephalitis (ME) hypothesis was proposed, many new findings and further hypotheses have been published that fit in with or support the ME hypotheses [71-73]. That is in agreement with our findings and it means that intervention in the early stages of the disease has become important, that period is called the critical period. It is believed that the prognosis of the disease will be different if that period is missed [74]. In this sense the importance of our findings can have practical applications in the prevention of the illness keeping in mind its direct relation to the aetiology and physiopathology of schizophrenia. The possibility to study the amniotic fluid cells by means of virological or electron microscopic techniques is suggested in

women at risk of having a schizophrenia offspring with the objective of applying preventive measures, previous information of the results, it would intend the voluntary pregnancy interruption or an early anti HSV1 treatment, if this viral infection is demonstrated in early neurodevelopment stages in the amniotic fluid cells.

## Acknowledgement's

We thank the Psychiatric Hospital of Havana and the National Institute for Scientific Research Research of Cuba for the scientific assistance and facilities for the realization of this research and the Faculty of Science, Málaga University, Spain, for the partial financial support for this work. The author has declared that there are no conflicts of interest in relation to the subject of this study.

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**DOI:10.31579/2642-973X/132**