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VIROLOGICAL AND IMMUNOLOGICAL INVESTIGATIONS IN SCHIZOPHRENIA

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The role of the infectious factors in the aetiology of schizophrenia constituted the subject of many investigations in the past. They have supposed the viral aetiology, too, without supporting this hypothesis by concludent arguments. Recent developments in virology, namely the discovery of the role of slow viruses in some mental diseases, gave new direction to these investigations. In the period 1975—1980, Tyrrell, Crow et al. demonstrated the cytopathic effect of the cerebrospinal fluid (CSF) of some schizophrenics and patients suffering from other mental diseases. Taking into consideration this hypothesis, since 1980 we have initiated a complex investigation using a group of schizophrenics in parallel with a control group coming from the Psychiatric Clinic of Tîrgu-Mureş. During this study we examined the cytopathic effect (CPE) of the CSF of these patients and examined the cell cultures by electron microscopy. These virological investigations were completed by immunological ones such as the determination of T and B lymphocytes, the nitro-blue-tetrazolium (NBT) test and the determination of circulating immune complexes.

Material and Method

We used in our study a number of 12 schizophrenics with an evolution of the disease under 2 years (between 2 weeks and 23 months). The diagnosis of schizophrenia was established on the bases of the OMS-IPSS criteria. The patients were included in the following clinical forms of schizophrenia: 6 cases of paranoid schizophrenia, 5 patients with hebephrenia and 1 case of schizophrenia simplex. The control group consists of 8 patients suffering from alcoholism, psychosis, psychopathy a.s.o. The CSF was collected through suboccipital puncture in sterile conditions and passed on KB cell cultures in a proportion of 2ml CSF to 18ml cell culture, cultivated with M_{199} growth medium, 10% bovine serum and

antibiotics. The cell cultures were kept on 37°C and checked daily through 7 days in order to determine the CPE. From the cultures with an evident CPE, a part was passed again on KB cells in the proportion mentioned above, in order to follow the transmisibility of the agent. The cultures then were sectioned and prepared for electronmicroscopic investigations made with a TESLA BS 613 microscope. As latent viruses are present in cell cultures under the form of a genom in defective state, to exalt the CPE, we used the method of *László* et al., which consists in the pretreatment of the cell culture with adenovirus 3 and after that with the pathologic product.

Discussion and Results

The CSF of the 12 schizophrenics had a CPE in 99.66% of the cases (11 patients of 12). This CPE was evident at the fourth passage in 5 patients and less evident in 6 cases. These results confirm the fact that in the CSF obtained from schizophrenics there is a transmissible agent. The CPE appeares in 6—9 days from the inoculation, but it does not look like at the second passage was present in 3 cases (37.50%). The electron- at the second passage was present in 3 cases (37,50%). The electronmicroscopic investigations proved the existance of some virus like particles in 7 cases in the schizophrenic group and 2 cases in the control group. In one patient from the control group we found in the CSF herpesvirus. The viruses found in the schizophrenics and the two patients from the control group have a size of 30—45 nm, an electronoptic dense core and a cover like ARBO-viruses. Among the mature particles there were immature ones, too, without a central core. The presence of the particles was proved more easily by the method using the helper virus. The determination of the circulating immune complexes present in the alpha—2 globulin in the schizophrenic group gave the following results: the complexes were present in 100%, having as antigenic component DNA. Among the immunglobulinic components of the complexes we found IgG in all cases, IgM in 9 cases, IgA in 3 cases and C_3 in all cases. These results plead for an affection in which the body produces antibody against the pathogen agent, but cannot neutralise the virus, and gives rise from the viral antigen and antibody to the mentioned immune complexes.

The NBT test was effectuated in every patient from both groups. The normal values are 10—20%. The results were much higher in the schizophrenic group but were normal or slightly elevated in the control group (2 cases). The small number of cases does not permit an adequate statistical evaluation. In the schizophrenic group the arithmetical mean was $= 46.25\%$ and the standard deviation $s = \pm 23.81$. At the P threshold we found that this is over 0.50. It seems to us very interesting that the patients with high NBT values (between 68 and 80%) were schizophrenics with an evolution under 3 months. The elevation of the NBT values can be explained with the fact that when the oxidative metabolism of

the neutrophils is stimulated by the presence of an infection or antigen-antibody complexes of high molecular weight such as the circulating immune complexes, the number of the neutrophils which reduce NBT in vitro increases.

We tested the proportion of T and B lymphocytes too (normal values T = 40—45%; B - 30—35%). The values obtained in the schizophrenics were much more dispersed, the B lymphocytes having a slightly elevated value (x = 36,33%), while the T lymphocytes had a slightly lower value (x = 38,54) The results obtained in the control group are also insignificant. The slightly elevated values of the B lymphocytes show an increase of the antibody activity, while the slightly low T lymphocyte values show a discrease of the cell mediated immunological responses.

Conclusions

In spite of some not quite concludent results, we could summarize our conclusions under the form of a hypothesis. In our opinion the principal aethiological factor in schizophrenia could be a virus. This virus could be responsable for the presence of some circulating immune complexes which modify the oxido-reductor activity of the neutrophils, all these phenomena being accompanied by the slight increasing of the antibody activity and descreasing of the cell mediated immunological responses. Taking these into consideration, we propose the utilisation of levamisol as adjuvant drug in the treatment of schizophrenia, because it helps in the synthesis of the interferon, being an immune regulator of the T lymphocytes. The hypothesis of the viral aethiology seems to be in contradiction with the hypothesis of the hereditary predisposition. The transmission of the predisposition as a genetic defect creates in our opinion a "locus minoris resistentiae", where under some special circumstances the virotic particles act and give rise to the manifest disease.

References

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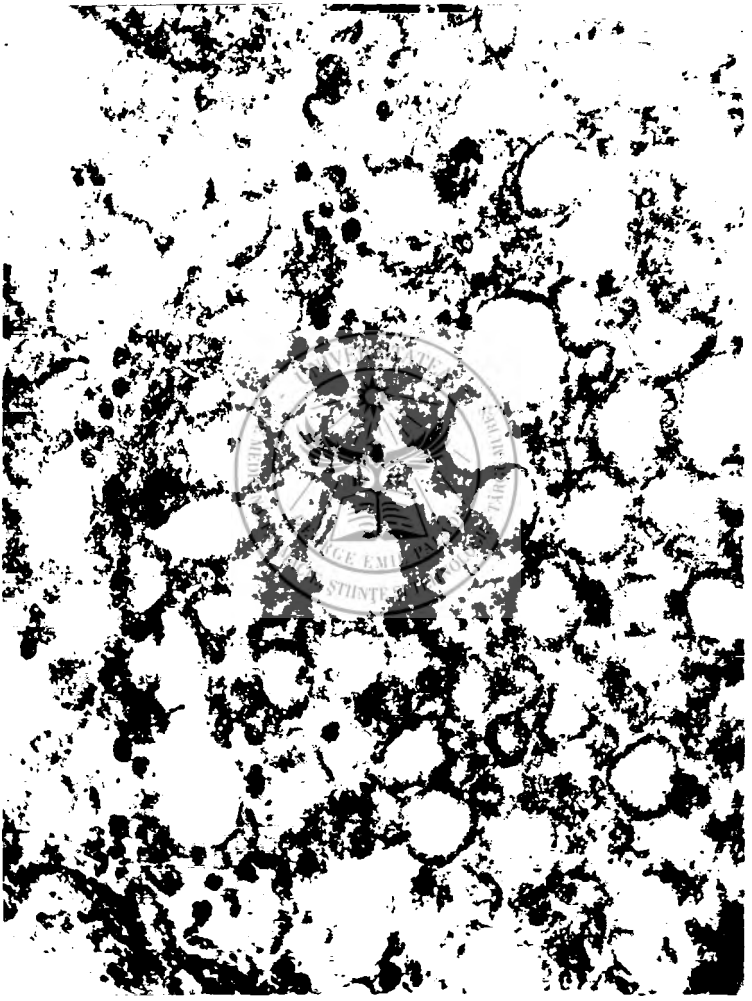

Fig. 1: Arbovirus-like particles in citoplasm of KB cell line, after inoculation with cerebrospinal fluid obtained from a patiens with schizophrenia diagnosis (80.000 x).

Fig. nr. 1: Lotul tratat cu clorură de dicloracetil 5%. Imagine dintr-un lobul hepatic cu aspectul normal. Col. HE, ob. 20×

Fig. nr. 2: Lotul martor. Aspect al spațiului port cu infiltrat inflamator cronic. Col. HE, ob. 20×

Fig. nr. 3: Lotul tratat cu clorură de dicloracetil 1%. Spațiu port lărgit, infiltrat cu o celulariație inflamatorie de tip cronic. Col. HE, ob. 20×

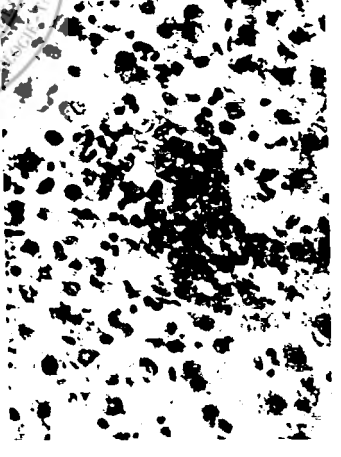

Fig. nr. 4: Lotul tratat cu clorură de dicloracetil 5%. Prezența aceloraşi microfocare inflamatorii ca la loturile anterior care. Col. HE, ob. 20×