CHROMOSOMAL STUDIES IN THE COURSE OF SCHIZOPHRENIA

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Populational genetics failed to solve definitety the problem of the role of hereditary factor in the etiology of schizophrenia. No clean Mendelian pattern has been found for either recessive or dominant heredity of the illness.

The discovery of a method for microscopic observation of human chromosomes resulted in the intensive penetration of cytogenetic investigations into all the fields of pathology, psychiatry included.

In schizophrenics examinations on a large scale have been carried out by the sex-chromatin method, combined in certain cases with cytogenetic explorations. The latter were usually accomplished upon a small number of patients. Some authors reported a greater frequency of deviations in the number of sex-chromosomes, as well as non systematic structural chromosome changes — A. Kaplan and J. Cotton (12), J. Dasgupta, D. Dasgupta and M. Balasubrahmanyan (4). Numeral aberrations and chromosomal breaks and fragments were found by J. Anders and coll. (1), A. Kaplan (13). M. Tzoneva-Maneva and M. Kratchunova (22) and V. Jontchev and coll. (11) also found a higher percent of chromosomal abnormalities (in number and structure) but with statistical significance only as far as polyploidia is concerned. Other authors (J. Book, S. Nichtern and E. Gruenberg — 2, T. Raphael and M. Shaw — 17, J. Nielsen and M. Fischer — 16, M. Wolreich and coll. — 23) don't mention chromosomal aberrations in the cytogenetically examined schizophrenic patients. In these not so numerous cytogenetic investigations the accent is laid upon the search for specific systematic chromosome anomalies. Besides, in nearly all the cases the patients under investigation are chronics and have long before been hospitalised.

We carried out our first cytogenetic investigation of schizophrenia in 1965 (together with M. Tzoneva-Maneva and B. Petrov) upon 10 patients with «family» schizophrenia. We didn't find one type aberrations but 2 cases of XY/XXY mosaicism, one of them with clinical features of Kleinfelter, and chromosomal lesions of the rate of breaks fragments and one translocation in 6 of the patients. Next (M. Tzoneva-Maneva, L. Ivanova and B. Petrov — 21) we examined the schizophrenic and healthy individuals from three generations of a family with numerous cases of schizophrenia. We found chromosomal damages only in two cases which were in an acute stage of the disease and under neuroleptic treatment at the moment of examination. So we directed our following investigations along two lines: the correlation between the stage of the psychosis and the chromosomal lesions (5, 6) and the role of the neuroleptic treatment in this connection (8, 9, 10).

In this report we present the results of the cytogenetic investigation of 50 schizophrenic patients — 26 women and 24 men at the age from 17 to

70 years average 29.5 years). For clinical characteristics A. V. Snezhnevsky's (19) classification was used: 29 patients had the periodic form

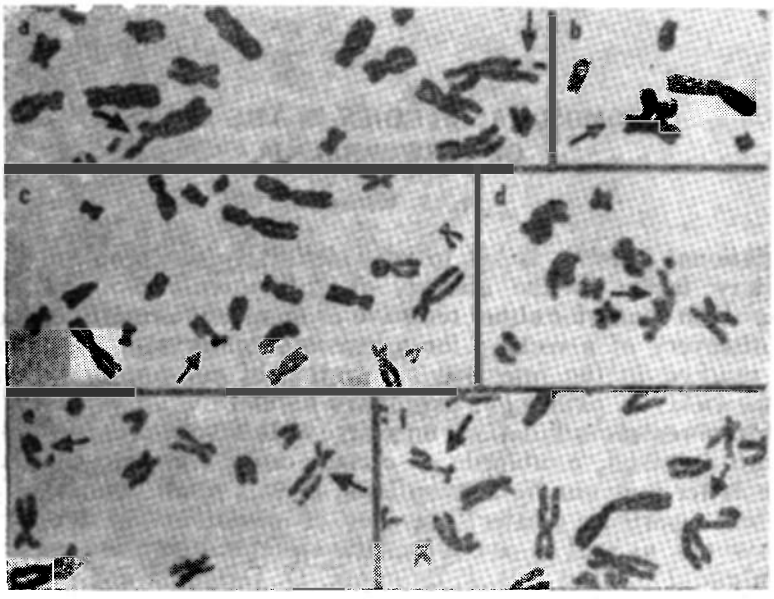

Fig. 1. Partial cells with various chromosomal abnormalities from acute schizophrenic patients before treatment: a, c, d, f — chromatid and isochromatid breaks; b — quadriradial figure; e — chromatid break and gap.

with clear remissions between the attacks), 15 — the intermediary and 6 — the continuous one. All of them have been under observation from 3 to 10 years. Twenty of the patients with periodic form and 12 of those with intermediary form have more than one attack before or after the cytogenetic examination. Every single patient was examined first in the active (initial) stage of the psychosis (or the respective attack) before the beginning of any treatment or Rö examination, (some of them once again in another attack), and 22 — once again during the remission. In every case intercurrent somatic diseases were excluded, and so was neuroleptic influence. Eighteen patients were examined in the first month of the disease and 26 — in the first month of the respective attack.

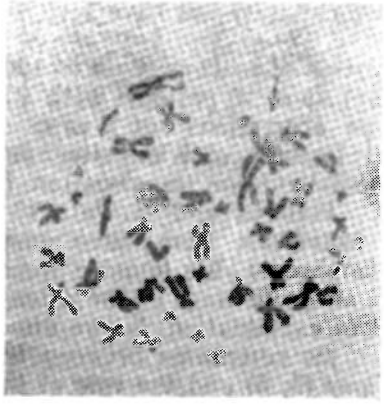

Fig. 2. Cell with chromatid break.

In the chromosomal study metaphase figures of short-term leukocyte cultures obtained from peripheral blood after the method of P. S. Moorhead and coll. (15) were)

used. Only cells with no less than 44 chromosomes were studied. The analysis was carried out on photocopies, and supplemented when necessary with microscopic inspection. Breaks were diferentiated from gaps by the dislocation of the fragmented parts along the length or the axis of chromatids. In the calculation of break level breaks, deletions, fragments, dicentrics and ring chromosomes were included, the pathological character of the gaps being not confirmed according to the opinion of most of the authors. Every structural change was counted as one number regardless of whether one or both chromatids were affected.

Altogether 80 examinations were carried out. Every single examination comprises an average of 91 cells (in the limits between 50 and 140) or a total of 7 266 cells from schizophrenic patients were analysed.

A control group of 18 individuals (healthy and neurotics) were studied in the same way with an average of 98 cells per examination and a total of 1759 cells.

Statistically the methods of alternative and variation analysis were used.

Our results confirm the absence of systematic chromosome aberrations in schizophrenia. In the active stage of the illness a considerably greater frequency than in the controls (statistically reliable) was observed of the following changes: aneuploidia in the direction of hypodiploidia, structural chromosome damages such as breaks, fragments, more rarely deletions and very rarely chromosome transformations-(dicentrics and ring chromosomes) (table 1). Chromosomal damages found in this investigation are presented on fig. 1.

As the 360 cariograms made in 11 of the patients show, neither hypo — nor hyperdiploidia are related to mono-or trisomia of certain chromosomes

As the psychotic attack subsides these structural changes decrease in number; in the remission their frequency is considerably lower: from 13.9% cells with breaks to 7.9% ($P<0.001$), and from. 0.18 to 0.10 average number of breaks per cell ($P<0.001$), as seen in table 2. No significant differences between active stage and remission were found in the other values.

In this manner a correlative dependence of the chromosome damages is found out in the first place with respect to the stage of the illness and, only to a certain extent, with respect to its clinical form. Differences between the periodic and the intermediary forms are observed with respect to the rate of decrease of the structural chromosome changes during remission (the decrease is less pronounced in the intermediary form). In continuous schizophrenia cases, during the first year no considerable differences are found, as compared to the two other forms (with the exception of a more frequent polyploidia); in later stages a tendency toward a decrease of the chromosomal damages is also observed here (regarldless of the active psychotic production).

The chromosomal damages are most pronounced during the earliest periods of the disease, as well as in single psychotic attack. In this respect of special interest are the exminations in 4 cases, which, being intended for control investigations in remission, coincided with the first «prodromal» manifestations of a new attack. They revealed a tendency toward a sharp increase of the chromosomal structural changes at the first signs of deterioration of the patient's mental state. These damages are even more pronounced than those during the preceding attack, which is due probably to the fact that the causing factor has the greatest effect upon the organism before the appearance of the manifest psychotic symptoms.

Table 1

	sch	controls
Number of patients examined	50	18
Number of examinations	55	18
Total cells examined	5124	1759
% hypodiploid cells	11.3	6.4
% hyperdiploid cells	1.6	1.2
% tetraploid cells	0.5	0.5
Gaps	353	79
Breaks	629	39
Deletions	36	6
Fragments	261	14
Dicentrics and ring chromosomes	7	—
% cells with breaks	14.1	3.1
Average number of breaks per cell	0.18	0.03
% cells with structural damage	18 3	6.8

Table 2

	Active stage	Remission
Number of patients examined	22	22
Number of examinations	22	25
Total cells examined	2134	2142
% hypodiploid cells	12.0	11.1
% hyperdiploid cells	1.2	0.9
% tetraploid cells	0.4	0.7
% cells with breaks	13.9	7.9
Average number of breaks per cell	0.18	0.10
% cells with structural damage	17.9	11.6

Irrespectively of the general tendency toward a higher level of chromosome damage in the active stage of schizophrenia individual differences between the patients exist. There are cases with a very high rate of damage and others without great deviations or even without any. In 2/5 of the examinations in an active stage the rate of cells with breaks does not exceed 10% but in the rest 3/5 it exceeds this value being more than 20% in 12 patients.

The absence of a system in the damages observed during this investigation, and their dynamics give us grounds to assume that they are not initial, primary, but secondary and are caused by the basic illness.

It is very difficult to answer the question about the intimate character of the damaging effect upon the chromosome set, schizophrenia being still an illness with unclear etiology and, to a certain extent, pathogenesis. It would be logical to look for an explanation in the toxic influences of the patient's serum, having in mind that according to one of the most popular conceptions of the nature of schizophrenia it is an endotoxicosis and that the toxic effect of schizophrenic patients' serum has been proved many times upon various biological test-objects.

Some investigations on the effect of biologically active substances from the esrum of schizophrenic patients upon cellular microstructures are in favor of

this view. V. Romasenko (1967) found a reduction of the concentration of ribonucleoproteids and a sharp change in the mitochondria in the rat cortex cells; G. Kobrinsky, I. Domashneva and T. Loseva (14) observed inhibition of the cells' mitotic activity in Hela and Hep tissue-cultures.

It is particularly interesting to compare our data with the investigations of V. Buravliov (3). He has observed a reduced mitotic index and a rise in the frequency of chromosome breaks in cultures of brain tissue from embryos of schizophrenic mothers, as well as in brain tissue cultures from embryos of healthy mothers, after treating them in vitro with serum from schizophrenic patients.

Describing the pathogenic (for the chromosome set) factor generally as a toxic one, we are unable to draw conclusions about its intimate nature from the kind of chromosome changes. On the basis of literature data it may be assumed, that such changes might be the result of an endotoxicosis (regardless of the nature of the endotoxic factor), as well as of autoimmune processes or virus infection.

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ИЗУЧЕНИЕ ХРОМОСОМ ПРИ ШИЗОФРЕНИИ

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РЕЗЮМЕ

Проведены цитогенетические изучения культуры лейкоцитов в периферической крови у 50 больных с шизофренией в активной, начальной стадии психоза или в период приступа, и повторно у 22 этих же больных в период ремиссии.

При активной стадии шизофрении, наблюдаемые повреждения хромосом в виде разрывов, фрагментации, редко делеций и совсем редко хромосомной трансформации встечались значительно чаще, чем в контрольной группе из 18 человек. Уровень этих хромосомных изменений значительно ниже у этих больных, исследованных в период ремиссии. Особенно значительные изменения хромосом найдены у больных при первых «продромальных» признаках нового приступа.

Отсутствие системности в наблюдаемых при этом исследовании повреждениях и их динамика дает основание считать, что они не первичные, вторичные и вызваны токсическими (или другими неизвестными этиолоа гическими факторами) воздействиями на основное заболевание.