SERUM ANTIBODIES TO BRAIN PROTEIN ANTIGENS IN INFANTILE CEREBRAL PALSY

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Establishment of the unique features of the immune status of the developing organism is known to depend not only on its genetic attributes, but also on various epigenetic causes. Among the latter, an important or possibly leading role is played by the character of the mother's immune status during pregnancy: on immunization of pregnant animals with any antigens their offspring acquire a lasting change in their ability to give an immune response to the particular antigens. Moreover, probably depending on the dose of the antigen, its nature, and the number and times of its administration, either marked depression [7] or considerable enhancement [4] of the primary and/or secondary immune response to an injected antigen may be observed in the progeny of the immunized mother. It has been suggested that the immune status of the pregnant mother and, in particular, relations between individual sets of idiotype-anti-idiotypes, directly affects the developing repertoire of the offspring's immunocompetent cells [6, 8].

The clinical consequences of this, as applied to man, may be extremely important. To begin with, in the context of formation of the fetus and the individual features of the state of a child whose mother has certain permanent or transient autoimmune disturbances. We may recall that the immune system as such, besides its protective role (against external antigenic stimuli), is involved in processes of differentiation and morphogenesis [1]. The morphogenetic activity of the molecular factors of the immune system has been demonstrated in numerous studies [1, 3]. Transplacental passage of antibodies, including those aimed at brain-specific proteins, also has been described, and this phenomenon may be connected with the causes of development of disturbances of the fetal nervous system [3]. In this connection, considerable deviations from normal immune homeostasis in the mother may be fatal for the fetus or may lead to considerable disturbances of its development.

The severe and ever more widespread form of developmental pathology such as infantile cerebral palsy (ICP) can serve as one possible example. The bases of the etiology and pathogenesis of ICP still remain a topic for discussion. However, the study of the mechanisms of this disease (or of certain of its forms) from the standpoint of a disturbance of immune homeostasis and, in particular, induction of "antibrain" autoimmune processes, disturbing the course of normal morphogenesis and differentiation of the nervous system of the fetus and child, is in our view most convincing [3, 5].

In this paper we attempt to analyze deviations in the composition of circulating "antibrain" autoantibodies in children with the diagnosis of ICP and to assess the degree of their similarity with maternal autoantibodies.

METHODS

Blood sera of children (n = 75) suffering from ICP, between 2 and 7 years of age, and also three mother—sick child pairs (age of the mothers 24-36 years, age of the children 1-3 years, with a diagnosis of ICP or spastic diplegia).

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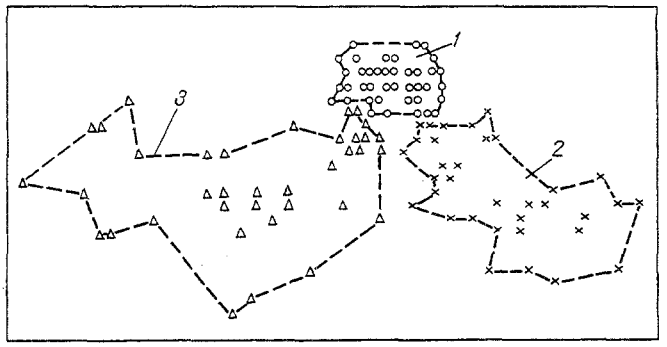

Fig. 1

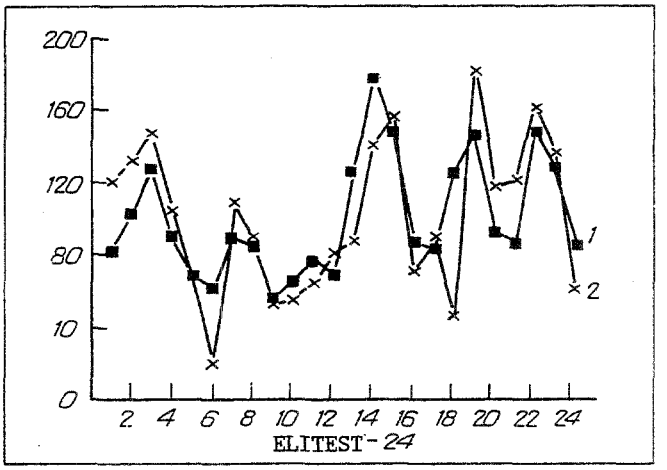

Fig. 2

Fig. 1. Characteristic groupings of populations of "immunoreactivity points" of healthy persons (1) and patients with ICP (2) and multiple sclerosis (3). Each point reflects the projection of the results of integral analysis of "spectra" of immunoreactivity of an individual serum with each of the 24 components of the ELITEST-24 test system on the display screen. The results were obtained by analysis of immunoreactivity "spectra" of the corresponding sera with the aid of the VISUAL program. The high independence of all three populations of points, evidence of a high degree of specificity of humoral autoimmune processes in the corresponding diseases, will be noted.

Fig. 2. Comparison of levels of "antibrain" immunoreactivity of blood sera in mother and child pair (with diagnosis of ICP). Abscissa) serial number of antigenic components of ELITEST-24 test system. Ordinate) level of immunoreactivity (conventional units). 1) Immunoreactivity of child's serum with each component of test system; 2) data on immunoreactivity of mother's serum.

Samples of sera were obtained from the No. 18 City Special Psychoneurological Children's Hospital (Moscow). Sera (n = 80) obtained from physically, neurologically and mentally healthy donors, were used for comparative analysis.

Autoantibodies in the sera were determined by solid-phase enzyme immunoassay, by the usual methods on standard 96-well Cook Microtiter EIA planchets (Dynatech, Germany), using as antigens the 24-component ELITEST-24 test serum (USSR Author's Certificate [2]), containing brain protein antigens, isolated by means of a specially developed version of the readily standardized preparative isoelectric focusing, and incorporating both monospecific and general tissue proteins (total Triton/urea brain extracts, fractionated within the pH range from 3.5 to 9.5). The immunoreactivity of the test sera was characterized by a set of 24 numbers (conventional units of immunoreactivity), proportional to the content of autoantibodies to each component of the test system (each of the 24 components consisted of a highly reproducible set of several tens of unidentified brain proteins, and it differed from every other component in the values of pI of its constituent proteins [2]). The data were analyzed with the aid of specialized computer programs (VISUAL and DIAGNOST) written by B. B. Kloss (Programprom Research-Production Combine, Moscow) and adapted for ELITEST-24 technology. These programs were based on the use of the "chief components method" and of linear discriminant analysis. The programs made it possible to assess the overall qualitative character of immunoreactivity patterns of the test sera with antigens of the ELITEST-24 test system and to undertake "diagnostic classification" of the test samples of sera. Calculations and illustrations were done by the use of an AT PC computer (IBM, USA).

RESULTS

With the VISUAL program it is possible to present a 24-dimensional pattern of immunoreactivity, characterizing the test serum, in the form of a point in two-dimensional space on the display screen. Figure 1 shows a two-dimensional projection of immunoreactivity of blood serum samples from tested patients with ICP on the computer screen, and

for comparison with corresponding populations, "immunoreactivity points" of healthy individuals and of patients with multiple sclerosis. The illustration clearly demonstrates a deviation from the normal level of reaction of serum antibodies with brain proteins (with components of the ELITEST-24 test system), characteristic of children with the diagnosis of ICP, and it demonstrates the marked specificity of their antigenic trend compared with that of autoimmune brain diseases such as multiple sclerosis. Incidentally, if the DIAGNOST program was used at the same time, it enabled children with ICP and children with multiple sclerosis to be classified in 100% of cases in accordance with their diagnosis (and also in 80-100% of cases, patients with epilepsy, with hepatocerebral dystrophy, and with schizophrenia) to be diagnosed differentially (blood sera from the corresponding patients, totaling 40-60 samples, were obtained from the Institute of Neurology, Russian Academy of Medical Sciences, and the No. 4 City Psychiatric Hospital, Moscow).

In three cases we were able to compare the characteristic spectra of immunoreactivity of the blood sera both of children with ICP and of their mothers. The results of this comparison are given in Fig. 2. When they are analyzed, attention must be paid to the marked similarity in the trend of the antibodies to particular components of the ELITEST-24 test system, characteristic of each individual mother and child pair.

The results probably indicate that congenital or acquired deviations from the normal level of maternal immune reactivity relative to her own nervous system antigens are epigenetically "inherited" by her child.

It will be evident that the formation of a pathological repertoire of "antibrain" antibodies, constantly present in the fetus and induced by the mother, cannot but affect the formation of the fetal nervous system at the stages of ontogeny (at the "critical" periods of embryogenesis and the early postnatal development of the nervous system). It can be tentatively suggested that in cases of a pathologically high level of production of these antibodies or if the capacity of the compensatory mechanisms is lowered, this initially latent situation (the mothers of the affected children had no clinically apparent neurological abnormalities) may lead to the formation of neurological symptoms and syndromes characteristic of ICP.

To sum up the foregoing facts, it must be emphasized that ICP, as a separate although complex nosologic unit, is characterized by the presence of a special spectrum of autoantibodies, highly characteristic of this disease and different in its antigenic trend from autoantibodies discovered in other nervous and mental diseases, in the blood of the affected children. The characteristic antigenic repertoires of the corresponding autoantibodies in this case are formed in children in the prenatal and/or postnatal period, and they are largely under the influence of the individual nature of the antigenic trend of the antibodies (idiotypes and anti-idiotypes), present in the mother during pregnancy.

It can be postulated that pathological changes in the immune status of the fetus and child, accompanied by hyperproduction of "antibrain" autoantibodies, may be connected causally with ontogenetic disturbances of formation of the nervous system, expressed to different degrees. The problems of the identification and functional characteristics of specific target antigens of brain tissue (not identified in this study) in ICP, which is important from the standpoint of possible prevention or early correction of the corresponding pathological forms, is still open and requires further research.

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