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Clinical and Immunological Aspects of Resistant Epilepsy in Early Age Children.

Dinmukhamed Ayaganov^{1*}, Marzhan Lepessova², Gaukhar Abassova¹, Alma Issabekova², Bakhytkul Myrzaliyeva², Elmira Amanova¹, and Gulmariyam Zhainazarova¹.

¹International Kazakh-Turkish University named after H.A. Yassawi. Republic of Kazakhstan, PC 161200, Turkestan, 29, B.Sattarkhanov avenue.

²Kazakh medical university of continuing education. Republic of Kazakhstan, PC 050057, Almaty, 34, Manas str.

ABSTRACT

The purpose of our work is to analyze the clinical, electrophysiological, neuroradiological and immunological characteristics of epileptic encephalopathies in early age children and develop the criterion of early diagnostics. The results of examination of 183 children under 36 months with 135 children of resistant and non-resistant epilepsy are reflected in this article. The cogent correlative indicators of autoimmune changes in genesis of severe and resistant forms of children's epilepsy are received. The increase of pro-inflammatory interleukin-2 and S-100 protein in cerebrospinal fluid in correlative dependence is comparable with severity children's epilepsy. The dilated immunological examinations of cellular and humoral links of immunity with evaluation of a cytokine profile in children with parallel indicators of serum and cerebrospinal fluid are conducted.

Keywords: epilepsy, children, resistance, immunoglobulins, cytokines, antibodies, S-100 protein, DNA.

**Corresponding author*

INTRODUCTION

Topicality and epidemiology

In spite of the fact that epilepsy is known since the ancient times, there is a doctrine of unresolvedness and controversial issues of this disease. One of the most difficult problems is a new version of the epilepsy's pathogenesis. Epilepsy is a chronic disease of a brain taking the third place in the structure of children's diseases bringing to early neurologic disability. The disease is characterized by the repeated, not provoked seizures due to excessive neural activity followed by polymorphism of clinical and paraclinical manifestations (Zenkov, 2010. P. 27-36, Michael et al., 2010. p. 34, Guseva and Gekht, 2011. P. 45-58). It is known that one seizure during the life is endured by 5% of the population, and 20-30% of patients have a lifelong format of epilepsy (Kissin, 2009. P. 6-12, Wolf, 2005. P. 7-9). Epilepsy belongs to the main diseases of pediatric psychoneurology because 70% of patients get it during children's and teenage age. The morbidity is rather high during the first months of life (Prusakov, 2004. P. 82-85). It is shown that the highest prevalence of epilepsy during the first year of life is about 120 incidents per 100000 people, during the teenage age it is 20 per 100000 people (Hauser et al, 2011). The prevalence of the disease fluctuates within 5-10 incidents per 1000 people (Kirayev and Voskresenskaya, 2008. P. 58-61). According to other investigations it is about 1.5 to 50 incidents per 1 000 people, but the majority of researchers did not exceed 15 incidents per 1 000 people (Huang et al., 2002. P. 345-346). The Kazakhstan researchers think that the prevalence of epilepsy in the Republic of Kazakhstan is about 2.3 incidents per 1 000 people (Kuralbayev, 1999. P. 25). The morbidity of epilepsy, excepting the febrile seizures and single paroxysms, is about 20 to 120 incidents per 100 000 people in different countries of the world (Tomson, 2000. P. 15-21). At the same time, there is no sufficient data about the resistant forms of epilepsy and epileptic encephalopathies particularly. It is known that 20 – 30% of patients with epileptic attacks will be considered as patients with resistant form of epilepsy (Belousova, 2009. P. 102-104, Lebedeva, 2007. P. 25-31).

Aspects of a pharmacoresistance

The etiology of epilepsy includes genetic, structural, metabolic factors, but sometimes the etiology is unknown (Jones et al., 2008). One of the etiological factors of the epileptic seizure is the genetic propensity for the most synchronization of brain neurons work. An additional factor of an epileptic genesis is a damage or congenital anomalies of brain cortex development. The frequent reason of the destructive disorders bringing to the formation of epileptic focuses are prenatal and perinatal harm. Etiological factors are not limited by these factors. The neurometabolic diseases, the tubercular sclerosis, the subacute encephalopathies, the organic cerebral syndromes, and above-mentioned genetic dependency contribute to initiation of epileptic encephalopathies (Zenkov, 2010. P. 27-36).

A pharmacoresistance epilepsy is the type of epilepsy when the seizures are sustained and the possibility of remission achievement is rather small in spite of taking other anti-epileptic drugs. Therefore, there is no possibility to achieve the permanent remission of epileptic seizures, taking two adequate and innocuous anti-epileptic drugs (Kwan et al., 2010. P. 941-1106). According to statistics, about 30% of patients with epilepsy remain pharmacoresistance who require special therapeutic and diagnostic attention (Kwan and Brodie, 2001). Frequent epileptic seizures have a great impact on the health of the people; they suffer from behavioral and cognitive complications leading to their disability (Guekht et al, 2010). Pharmacoresistance of any patient with frequent epileptic seizures must be assumed as soon as possible that is why it is necessary to follow the principles of medicaments' therapy, developed in the 1997th (ILAE Commission Report, 1997. P 1245-1250). It is necessary to admit that the improvement of patients' treatment with a true biological pharmacoresistance is extremely limited now (Moricawa, 2004. P. 7-8). It is known that inefficiency of one correctly prescribed anticonvulsive drug gives only 10 % of guarantee that the preparation of the second choice will be effective. The absence of the effect of the second option of the monotherapy gives the absolute resistance (Kwan and Brodie, 2005. P. 224-235). The specific problem presents the children's pharmacoresistance due to its age specificity, critical influence on epilepsy and the treatment of the child. (Aldenkamp, 2000. P. 2-7. Berney, 2000. P. 20-25).

Pathogenesis and epilepsy genesis

Epilepsy genesis as the pathogenesis essence of these forms of epilepsy consists in violation of various

mechanisms of a brain changing the balance of stimulating and inhibitory processes with formation of the systematic organization of interneuron activities (Zenkov, 2003. P. 9-21). Under the influence of some ions at the level of membranes of neurons, there is an instable potential of dormancy in the form of excessive depolarization. For the generation of impulses the operations of stimulating neurotransmitters are required, which define the character of the epileptic neuron, the elementary unit of the epileptic reaction (Zenkov, 2010). It should be noted that the pathogenesis of epilepsy pays attention to pathological neurogenesis where repeated epileptic seizures lead to post-natal proliferation of the distant neurons. The resistant character of severe children's epilepsies is connected with excessive expression of NMDA receptor, which explains the hyperexcitability and paroxysmal activity. In the zones of brain which are exposed to "stimulating bombing" with long-lasting epilepsy there are plastic changes of receptors promoting their constant hyperexcitability (Scharfman et al., 2000. P. 6144-6158). Not only the destructive changes lead to the brain epilepsy, but also the process of interneuron contacts violation with a failure of homeostatic mechanisms (Ereniyev, etc., 1990). There are three concepts of the neurons epilepsy: 1) the violation of membranes or neuron's metabolism; 2) the changing of the environment surrounding the neuron; 3) the deficiency of inhibition processes (Karlova, 1999). According to the latest data, it is known that the interaction of hereditary specified factor of predisposition, the factor of the damaging influences and the initiating factor lead to the formation of the epileptic center before the manifestation of a clinical epileptic seizures (Toropov, 1996). For transformation epileptogenic focus to actively epileptic center need a number of factors, breaking the architectonics of neurons. (Shmatko, etc., 1991). Last thirty years have crowned the progress in diagnostics and treatment of epilepsy though a third of patients remain resistant to treatment and has serious complications bringing to disability (Gusev and Gekht, 2011). The incurability is more typical for the early childhood. The immature brain is more subjected to resistance where the prevalence of stimulating neurotransmitters over inhibitory ones is experimentally proved. In addition, it is necessary to consider that the amount of neurons of the immature brain have been multiplied up three times before the physiological apoptosis (Zenkov and Prityko, 2003).

A neuroimmunopathology of epilepsy

The scientific investigation and intensive research of the mechanism of epilepsy and function of the central nervous system formed a theory of imbalance between stimulating and inhibitory neuromediators (Mumenthaler et al., 2004). Nevertheless, there is a group of 20-40% with medicament resistance (French, 2010). The considerable prevalence of medicament resistance suggests that these forms must have other mechanisms of resistance, which are unknown. This theory reveals the autoimmune mechanisms in a brain, which play an important role of epilepsy genesis (Zarczuk, 2010). The sustained existence of the epileptogenic focuses demonstrates the autoimmune changes blocking the normal synthesis of gamma aminobutyric acid GABA (Peltola et al., 2000). The inflammation of these zones play a very important role in pathogenesis of epilepsy. The experimental models show that mediators of the inflammation possess pro-convulsive properties. The connection between cytokine and neurotransmitter systems is also presented (Vezzani and Granata, 2005. Bernardino et al., 2005). After the influence of unknown factors the glia with the strengthened release of the pro-inflammatory cytokine damaging the permeability of the blood-brain barrier (BBB) increases the level of calcium in the cell and modifies "the potential - dependent" ion channels. Besides, pro-inflammatory cytokines inhibit the absorption of the neuromediators in glial tissues, limiting the recirculation of GABA-receptors (Riazi et al., 2010. Vezzani et al., 2011).

Recently the appropriate works appeared about interrelation of immune system with nervous system, especially with epileptogenic system. So, the homeostasis of the organism is supported by neuroendocrine and immune systems (Howland and Psuchosoc., 2014), which is supported in recent years with the concept of an immunological background of some types of epilepsy (Zarczuk, 2010). The developing brain is the very sensitive to any changes, bringing to violations of a neurochemical order. Immunocompetent cells by means of the receptors perceive the neuro regulatory "urges" during the contact with the fibers of the nervous system, at the same time T and B-lymphocytes and macrophages of the membrane distribute certain information receptors all over the neuro regulatory systems, influencing the immune response and secretion of interleukin. The production of interleukin is under control of peripheral and central nervous system (CNS), which regulate the cytokine under the influence of neuromediators (Safarova and Kuliyeu, 2010). Thus, the cytokines playing the role in a neuroprotection by inhibition of epileptic activity depend on the functional condition of neurons (Ravizza and Vezzani, 2006). In spite of some investigations about the role of cytokine in epilepsy, there are many questions demanding further studying and explanation (Zarczuk, 2010).

While the analysis of the autoimmune diseases a certain part belongs to immunoglobulins (Rabson and Royt, 2010). The analysis of the literature shows that IgA plays an ambiguous role in immunity and depending on the structural forms participates in suppression of the immune response of the inflammatory diseases and the immunosuppressive effect is directed on noninfectious agents (Brendtzaeg, 2010. Scurlock et al., 2010). The significant role in realization of the immune response in CNS (central nervous system) belongs to interferon formation. Interferon increases the activity of hypothalamic system and it is one of the factors of change of permeability of a BBB. It stimulates the formation of T-helpers with an obstacle of activation of T-cytotoxic subpopulations (Totolyan and Skoromets, 2004). The immune supervision in the brain and subarachnoid space creates the populations of T and B cells. The role of cellular elements of immune reaction of patients with epilepsy is one of the important questions demanding further consideration and explanation (Zarczuk, 2010). There are investigations devoted to the identification of the autoantibody of the brain; also, there are many works of identification of anti-brain antibodies, such as S-100 protein, antibodies to deoxyribonucleic acid, antibody to the main protein of a myelin. The analysis of the features of the neuro specific proteins as the markers of various pathological conditions along with other methods is one of the perspective directions (Markevich, 2005).

The presented facts and hypotheses dictate the need of practical realization by means of the early diagnostics and finding of early markers of resistance of epilepsy from a position of evidential medicine (Totolyan and Freydlin, 2000. Aicardi, 1996). From the point of view of evidential medicine, the strategy and tactics of treatment of epilepsy should be based on data of researches with the high level of substantiality. Unfortunately, we do not have enough specific researchers of children's epileptic syndromes (Hermann et al., 2012. Ramm-Pettersen et al, 2011). Therefore, in most of the cases the results of preliminary international consensuses of experts are still used as the guide of diagnostics (Gusev and Gekht, 2011).

MATERIAL AND METHODS

403 children with various forms of epilepsy have been examined. On the basis of inclusion and exclusion criteria 183 children under 36 months (boys – 108 (59%), girls – 75 (41%)) have been ranged into 4 age groups: the 1st group – from 0 to 6 months – 63 (34.4%) children, the 2nd group – from 6 to 12 months – 52 (28.4%) children, the 3rd group – from 12 to 24 months – 38 (20.8%) children and the 4th group – from 24 to 36 months – 30 (16.4%) children. They were also divided into 3 clinical groups: I – the main group (71-38. 8%) – children with resistant epilepsy, II – comparative group (64-35%) – children with epilepsy, but without resistance, III – control group (48-26.2%) – healthy children. The criteria of the exclusion were the existence of the acute, neuro infection and system diseases, children taking antibacterial or immunomodulatory drugs, children who are older than 3 years and children with temperature. All children had the neurologic survey, the assessment of the somatic status, the analysis of a semiology of seizures, the EEG monitoring, the brain MRI and the immunological investigations.

The EEG research was conducted with the help of "Encephalan" R-19/26 (Russia, Taganrog) apparatus. Registration of the EEG was carried out in accordance with international system of electrocardiographic lead of 10-20 Jasper in bipolar lead with 100-microwatt calibration of 10 mm and the speed of 30 mm/sec.

Brain MRI diagnostics was carried out on the apparatus of the SIEMENS MAGNETOM C (Germany). The power of the apparatus is 1.5 T. The examination had three projections: axial, frontal and sagittal. The ethickness of a cut is 4-5 mm. In case of necessity, the contrast substance and the scans in the vascular mode were injected. The duration of examination was 35-40 minutes.

The immunological investigations are used to study the cellular and humoral link of immunity, with an assessment of a cytokine profile.

- The cellular link was estimated by method of a direct immunofluorescence with the help of luminescent Olympus microscope with monoclonal antibodies of the LLC Sorbent (Institute of immunology, Moscow) production.
- The humoral link was estimated with the help of immunoenzymatic tests (USA).
- The cytokine profile was estimated with the help of immunoenzymatic tests "Immunochem" (USA).

In order to study the indicators of immune system, the blood sampling was made by 5 ml disposable syringe in sterile conditions with heparin addition. For immunoenzymatic tests, the blood without addition of anticoagulants was used.

For the identification of the amount of immunoglobulins in peripheral blood, the method of the immune enzymatic analysis was used.

The identification of the content of cytokines in peripheral blood. The number of cytokines in the serum of blood of the examined patients has been determined by method of the immune enzymatic analysis with a set of the 96 standard alveolar stripping plat with the adsorbed monoclonal antibodies against cytokines.

Antibodies were estimated with the help of immunoassay "Immunochem" (USA). The liquor was taken in sterile conditions of 1.0 ml.

The design of the research. The research is descriptive one; the selection is total and diametrical with application of a case control. The mechanical randomized method was used inside of the groups.

The verification of the clinical diagnosis was carried out according to diagnostic criteria of the International classification of epilepsies, epileptic syndromes and similar diseases (1989, New Delhi, the USA); report of ILAE commission of classification and terminology 2001 and the project of classification of epileptic syndromes of ILAE 2001.

Statistical method

The statistical analysis of the obtained digital data was carried out by the standard methods of variation statistics, the correlation analysis, parametrical and nonparametric statistics on the basement of SPSS 19.0 program. The arithmetic average selection, the error of the arithmetic average and a mean-square deviation were defined. Reliability of distinctions was estimated with the help χ^2 .

RESULTS AND DISCUSSIONS

Semiology of seizures and neurophysiology

The ranging according to the age (in months) has shown that the bigger percent of examination had the children till 1 year old (62.8%) as the most vulnerable age of epileptic encephalopathies.

The ranging according to the clinical groups has shown: I – the main group (71-38. 8%), II – comparative group (64-35%), III – control group (48-26.2%).

In structure of resistant forms of epilepsy (71) the West's syndrome (36-50.7%) prevailed, multifocal resistant epilepsy - (18-25. 4%), the *Lennox Gastaut's* syndrome - (12-16.9%), the Ohtahara's syndrome - (2-2.8%), the Dravet's syndrome - (3-4.2%).

The character of epileptic seizures of children with resistant forms of epilepsy in 80% of cases was presented by epileptic spasms; in 20% of cases were other types of epileptic seizures whereas in the compared group the epileptic spasms were absent, the above described data have found the reflection in figure 1.

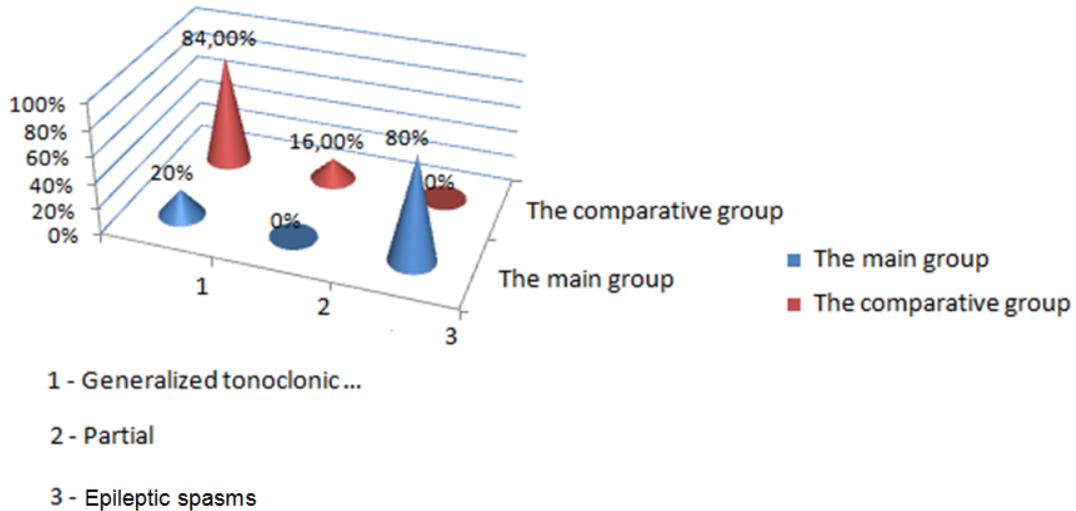


Figure 1 - Comparative characteristics of the types of epileptic attacks in children with epilepsy.

The following investigating phase of resistant forms of epilepsy was the electrophysiological analysis. The typical hypsarhythmia, the pattern "burst - suppression" and the multifocal centers of epileptiform activity peculiar for resistant forms of epilepsy, besides the regional sharp-slow-waves (SSW) were estimated in children of comparative and main groups. The children of control group did not show the epileptiform activity in 100% of cases. The figure 2 shows the structure of the epileptiform activity in children of the first 2 groups.

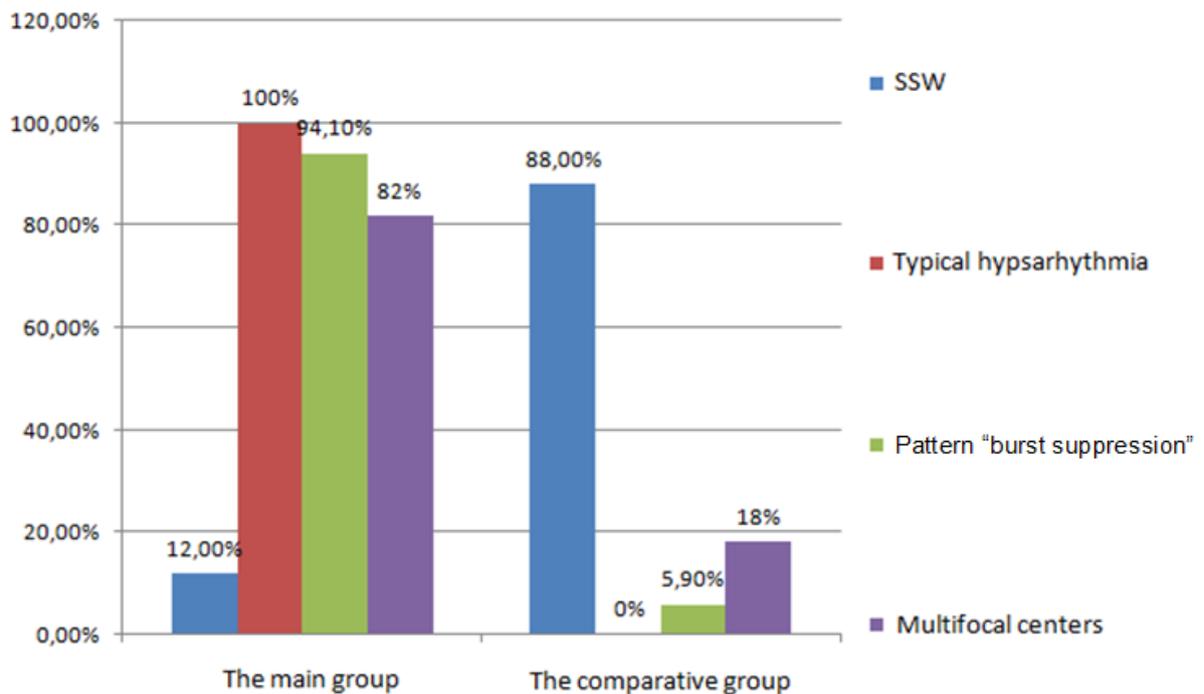


Figure 2 - Comparative characteristics of electroencephalographic parameters in children with epilepsy.

Figure 2 shows that indicators of a typical and atypical hypsarhythmia (100% and 94.1% respectively) prevailed in the main group, and also in 81.8% of cases the indicator of the multifocal centers has been identified whereas other types of epileptic activity has been shown in 12% of cases. At the same time the pattern of an atypical hypsarhythmia was among children with an early debut of a disease, on the average in 2.5 months, with prevalence of boys, with typical cluster epileptic spasms. The modified hypsarhythmia in the form of its variations is shown in EEG.

High positive correlative dependency ($r=0.65$) of an indicator of atypical hypsarhythmia in the main group and negative dependency ($r=-0.57$) in comparative group can be seen in the following figure 3.

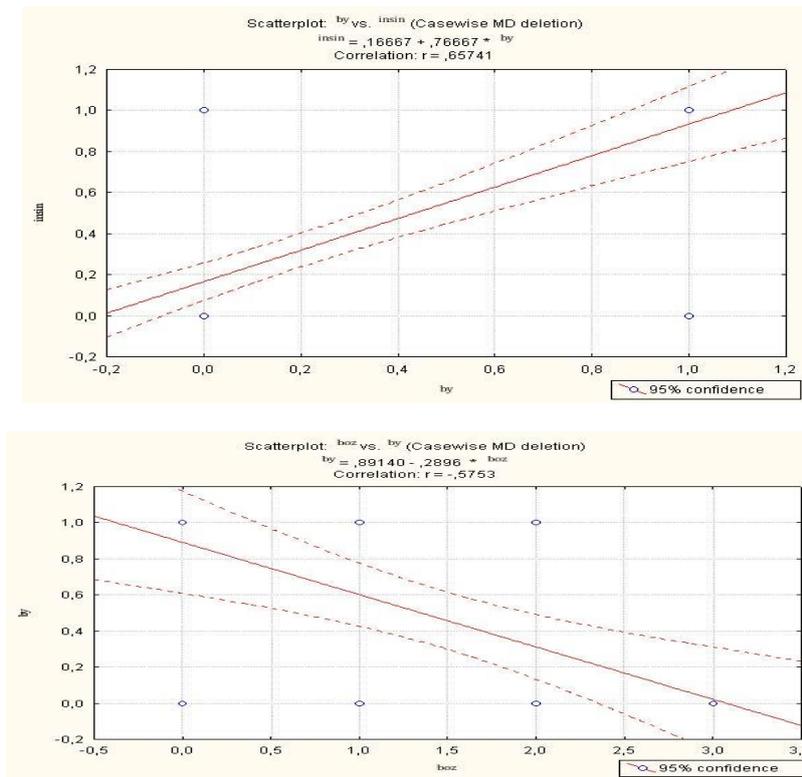


Figure 3 - Correlation dependency of atypical hypsarhythmia in children of the examined groups.

Neuroradiological characteristic

The following investigation phase – neuroradiological diagnostics. Results of this investigation phase are reflected in table 1.

Table 1. Neuro radiology characteristic of children with epilepsy.

Indication/groups	Main	Comparative	Control
Congenital malformation of CNS	33.3%	16.1%	-
Tuberose complexes	25%	6.5%	-
Atrophic modifications	20.9%	22.6%	-
Demyelinating modifications	4.2%	6.5%	-
Other findings	8.3%	25.7%	15.6%
Norms	8.3%	22.6%	84.4%

The analysis of this table shows the existence of rough modifications in a brain in the form of congenital malformations, the tuberose complexes in children of the main group.

Immunological researches

The immunological characteristic is presented in a following way: immunoglobulins, a cellular link of immunity, a cytokine profile, the circulating immune complexes (CIC), tissue specific antibodies for the brain substance (S-100 protein, antibodies to two-chained DNA). The received results are reflected in tables 2,3,4,5.

Assessment of a humoral link of immunity

Table 2. Immunoglobulin spectrum in children’s peripheral blood of the examined groups. Circulating immune complex (CIC) figures. Significant differences between the groups $p < 0.05$

Groups	Immunoglobulin			CIC N=до 55
	IgA (N=0.9-4.5)	IgM (N=0.6-2.5)	IgG (N=7.0-18)	
The main group (n=71)	2.54±0.12	1.80±0.06	11.23±0.56	88.4±0.5
The comparative group (n=64)	3.8±0.07	1.53±0.04	10.99±0.44	49.3±0.6
The control group (n=48)	4.2±0.06	1.28±0.07	9.18±0.56	43.2±0.5

From table 2 the reduction of the IgA level is visible, with rather normal amounts of IgM and a tendency of increase of the IgG level in children of the main group in comparison with comparative group. Apparently the indicator of the circulating immune complexes prevailed in the main group. In control group, the indicators demonstrated the norm.

The correlative dependence of the IgA content and the indicator of atypical hypersarhythmia in children of two groups can be seen in figure 4 where the children of the main group has the depression, in the comparative group the normal content of the immunoglobulin is noted ($r = -0.25$ and $r = 0.4$ respectively).

Assessment of a humoral link of immunity

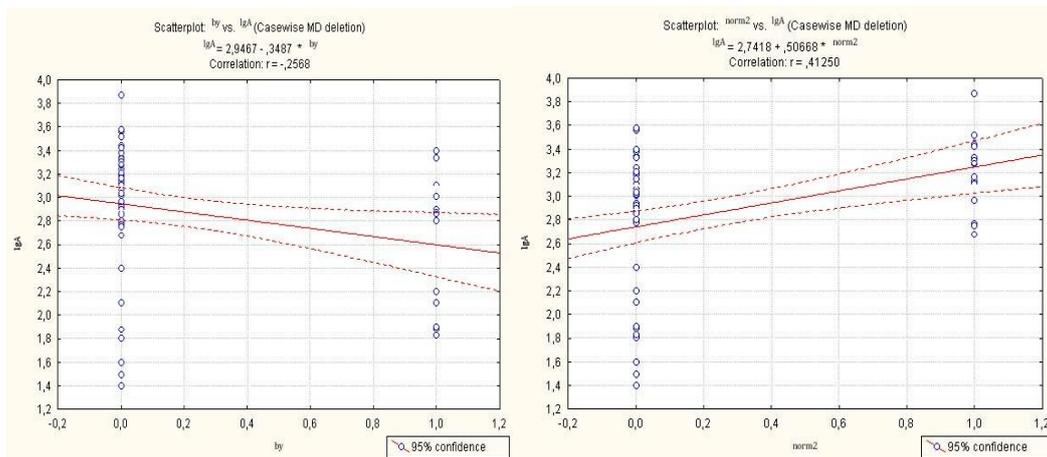


Figure 4 - The dependency of IgA content and the index of atypical hypersarhythmia in children of the examined groups

Cytokine profile

The analysis of a cytokine profile in children has shown certain changes, which have found reflection in the following table 3.

Table 3. The concentration of the main pro-inflammatory and anti-inflammatory cytokine in the serum of the healthy children and children with epilepsy. The validity with $p < 0.05$

Groups	Interleukin			
	IL-1 β	TNF- α	Interferon- γ	IL-10
The group of children with resistant epilepsy (n=71)	9.13±0.73	6.18±0.05	10.52±1.15	10.53±1.55
The group of children with epilepsy (n=64)	7.31±0.74	5.7±0.05	13.10±0.41	14.98±0.97
Control group (n=48)	6.28±0.32	4.89±0.08	9.34±1.01	17.45±1.98

The analysis of this table shows that in children of the main group the IL-1 β , TNF α levels are increased, IL-10 indicator is lowered, and the interferon level scale remains within normal amounts in comparison with other groups. These data have found reflection in figure 5.

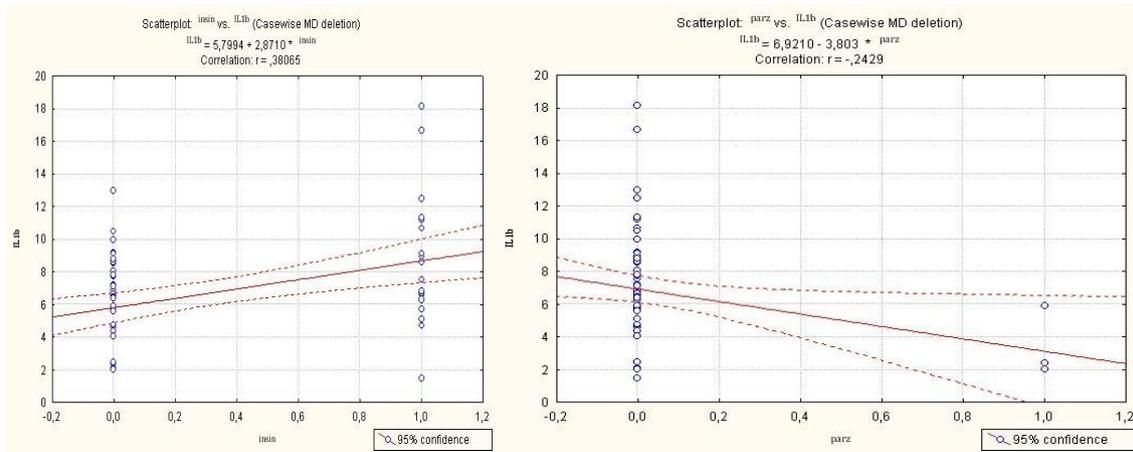


Figure 5 - The positive and negative correlation IL-1 β levels of the presence of infantile spasms in children of the main and comparative groups

The positive correlative dependency between indicators of IgG and TNF- α ($r=0.4$) as an indicator of synchronization of the epileptic center. See figure 6.

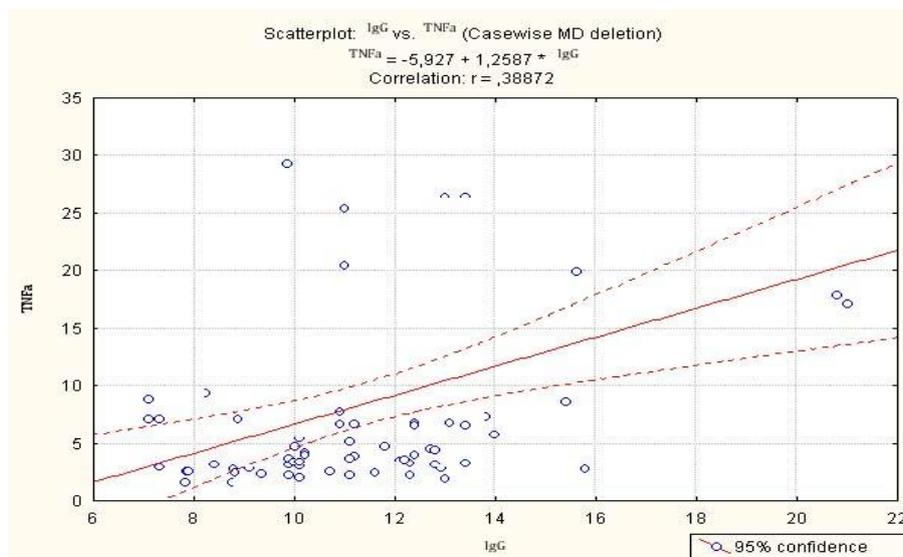


Figure 6. The correlative dependency between the IgG and TNF- α

CSF indicators

We have suggested the identification of IL-2, antibodies to two-chained deoxyribonucleic acid, S-100 protein in cerebrospinal fluid (CSF) in children of the main and comparative groups. In control group, the process did not take place due to ethical aspects. Results are reflected in the table No. 4

Table № 4. CSF indicators

The groups of children	IL-2	Protein S-100	Antibodies to DNA
The main group (40)	11.43±0.37	117.3±0.57	23.41±0.24
The comparative group (20)	5.34±0.26	75.4±0.45	1.91±0.38

The analysis of this table shows: the increase of pro-inflammatory interleukin, S-100 protein and antibodies to two-chained DNA in children of the main group.

Cellular link of immunity

The cellular link was estimated by the method of a direct immunofluorescence. The results of the research of a cellular link of immunity in children are reflected in the table No. 5.

Table 5 - The absolute number of subpopulations of lymphocytes in children with epilepsy and children of control group

Groups	Lymphocyte					
	CD3	CD4	CD8	CD16	CD72	CD4/CD8
The group of children with resistant epilepsy (n=71)	3.43±0.37	0.90±0.33	1.007±0.022	0.86±0.11	0.88±0.14	1.35±0.02
The group of children with epilepsy (n=64)	3.11±0.07	1.05±0.05	0.75±0.08	0.55±0.09	0.56±0.04	1.25±0.02
The control group (n=48)	2.01±0.09	1.15±0.04	0.99±0.04	0.44±0.07	0.49±0.05	1.29±0.01

We see that children of the main group have the decrease of the T-helpers, the activation of T-cytotoxic populations, the increase of natural killers and B-lymphocytes with an immune regulatory index whereas in children of control group the figures are different.

CONCLUSION

- The analysis of results of the examined children with epilepsy has shown that in the epileptic group the debut of a disease was various. The epileptic spasms unlike literary data were on average 2 months and 15 days (2.5 months) whereas the literary data shows the debut from 6 months age. The results of the conducted research demonstrate that the part of forms of epilepsies (West, Ohtahara syndromes) are transformed to severe epilepsy no only due to persistent morphological changes in a brain, but of caused autoimmune chemical violations.
- The electroencephalographic (EEG) characteristic is presented in the main group with reliable prevalence of the atypical hypsarhythmia and high correlative dependency (r=0.65).
- The main neuroradiological findings of resistant epilepsy were the rough morphological modifications in a brain in the form of focal cortical dysplasia, tuberose sclerosis complexes, various malformations and atrophic changes.
- Immunological disorders in children with resistant epilepsy were characterized by certain changes: IgA level depression with rather normal amounts of IgM and tendency of the IgG level increasing in children of the main group; increasing of pro-inflammatory cytokine level and the circulating immune complexes. In addition, the existence of autoantibodies to DNA and availability of S-100 protein in CSF in children with resistant epilepsy allow to admit their role in the genesis of the severe forms of this disease. A cellular link of immunity were characterized by the decrease of T-helpers, the activation of T-cytotoxic populations, the increase of natural killers and B-lymphocytes with an immune regulatory index. At the same time, the children of control group demonstrated different figures.

The received results testify the necessity of further research of this area.

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