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ETHIOPATHOGENETIC THERAPY OF HERPES VIRUS INFECTION WITH THE USE OF PROTEFLAZID

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List of abbreviations used

NK (CD16) — natural killer cells
NSE — neurospecific enolase
ME — meningoencerebritis
ANAD — acyclic nucleoside antiviral drugs
AB — antibody
AC — acyclovir
VZV — Varicella Zoster Virus
VSV — vesicular stomatitis virus
HHV6 — herpes virus 6
HHV7 — herpes virus 7
HHV8 — herpes virus 8
EBV — Epstein-Barr virus
HIV — human immunodeficiency virus
UQ — upper quartile
HSV1 — herpes simplex virus 1
HSV2 — herpes simplex virus 2
HV — herpesviruses
HVI — herpes virus infection
HG — Herpes genitalis
HE — herpes encephalitis
BBB — blood-brain barrier
HI — herpetic infection
GC — ganciclovir
DNA — deoxyribonucleic acid
ECG — electrocardiography
EMPR — encephalomyelopolyradiculoneuritis
TMP — total myelin protein
IFN — interferon
ELISA — Enzyme Linked Immuno Sorbent Assay
CT — computer tomography
MH — molecular hybridization
Me — median
MC — meningoencephalitis
MRT — magnetic resonance tomography
FAT — fluorescent antibody technique
LQ — lower quartile
NS — nervous system

NBT test — Nitro Blue Tetrazolium Reduction Test
AE — adverse effects
PCR — polymerase chain reaction
PT — Proteflazid
DEM — disseminated encephalomyelitis
CD16 — natural killer cells
CD20 — B lymphocytes
CD3 — T lymphocytes
CD4 — T lymphocytes-helpers
CD8 — cytotoxic T lymphocytes/suppressors
CVS — cardiovascular system
USI — ultrasound investigation
USDG — ultrasonic dopplerography
CIC — circulating immune complex
MCC — mononuclear cells cytotoxicity
CMV — cytomegalovirus
CMVI — cytomegalovirus infection
CNS — central nervous system
CPE — cytophatic effect
CN — cerebral nerves

INTRODUCTION

Rationale. In modern infectology herpes virus infections (HVI) hold one of prominent places both according to the variety of clinical forms and complexity of diagnostics and treatment. Among over 100 types of herpesviruses (HV) known at the present day, 8 types are human pathogenic: HSV1, HSV2, VZV, EBV, CMV HHV6, HHV7, HHV8 [44].

According to WHO data, from 65 to 90% of world population are infected with one or several types of HV, and from 2 to 12% of people suffer from herpes virus diseases on a world-wide basis [6, 52, 135]. HVI contamination and disease incidence are growing annually [114]. The similar unfavorable tendency is observed in Ukraine too [60, 79, 81, 115, 151]. The most important reasons for such an unpromising dynamics may be deemed increasing quantity of people with immune disorders within population, senior people, growing number of chronic diseases, unfavorable action of a range of ecological factors on human population, as well as the emergence of acyclovir-proof forms, HV mutants [141].

All HV types are characterized with long-term persistence in human body with the possible disease development even after the many-year latency period [132]. General pantropism of HV results in a significant polymorphism of clinical manifestations, complexity of pathogenesis and ability to affect almost all human body organs [44]. Against this background, NS damage with HV belongs to the most complex pathology [30, 55, 79, 200, 210, 214]. Hard progress, variety of neurological forms (encephalitis, meningitis, myelitis, neuroxitis), high probability of fatal results (up to 80%), patients' disability (50%), contamination of young and middle-aged people make it possible to consider the issue of herpes virus neuroinfections as not only medical, but also social problem [30, 55, 79, 83, 200, 214]. The forecast and result of disease course greatly depend on timely diagnosing and assignment of anti-viral therapy.

Notwithstanding existence of a variety of chemical anti-viral drugs, the issue of HI therapy remains to be open as before: there is no single drug or treatment regimen enabling to achieve reliable results, avoid complications and relapses of disease [81, 97, 134]. The therapy is complicated by the emergence of HV strains resistant to ANAD and insufficient efficacy of traditional treatment regimen for HVI chronic forms with relapses, in particular, for CMV and EBV infections [144, 153, 205].

In this connection, complex use of anti-viral and immunobiological (interferons, interferon inducing agents, immunoglobulins and immunomodulators)

drugs are being studied still to date; however, each treatment regimen has its advantages and disadvantages (toxicity, allergization, high cost of treatment).

In this regard, our opinion is that use of Proteflazid may be a prospective treatment option accostable to many patients.

Proteflazid is a domestic herbal drug, which contains flavonoids possessing anti-viral action (as a result of blocking virus-specific enzymes — HV thymidine kinase, DNA polymerase), interferon inducing (versus α- and γ-IFN) and apoptosis-modulatory activity [106, 109].

In this context we consider it being rationale to carry out enhanced study of therapeutic efficacy of Proteflazid in treating patients with HVI and develop mono- and complex treatment regimens capable to promote quality of treatment, reduce frequency of residual effects, relapses and costs of treatment.

Relation of work to scientific programs, plans, topics. The work was accomplished in the scope of Research Scientific Works of L.V. Gromashevskiy Institute of Epidemiology and Infektious Diseases of the Academy of Medical Sciences of Ukraine "Study of Pathogenetic Actions and Methods of Correcting Damages of Central and Peripheral Nervous System of Herpes Virus Etiology" (state registration number — 015U000016) in the intensive care, detoxication and neuroinfections medical units.

Purpose of study: To develop HVI (types I, IV, V and associations thereof) ethiopathogenetic treatment regimen using Proteflazid.

Objectives of study:

1. To study therapeutical, immunomodulatory, interferon inducing activity of Proteflazid in HV-infected patients.
2. To create mono- and complex methods of ethiopathogenetic therapy for various HVI clinical forms.

Study subject: patients with HVI; biological substrates (blood, blood serum, cerebrospinal fluid (CSF)).

Study object: etiology, pathogenesis, clinical manifestations of HVI; clinical and immunological efficacy of mono- and complex ethiopathogenetic treatment of HVI with PT with the use of blood ultraviolet irradiation.

Study methods: general clinical and laboratory methods; special immunological, immunobiological (ELISA); biomolecular (PCR); identification of

α- and γ-IFN levels in the course of disease; instrumental (brain and spinal marrow MRT); statistical methods.

Scientific novelty of study results.

PT influence on the clinical course, immunologic reactivity and dynamics of inducing interferon in patients with HVI was studied for the first time. It was proved that PT reduced toxicity and enhanced efficacy of anti-viral therapy. Interrelation was established between the flow of interferon conversion and improvements timing.

Indications and dosage regimens of PT with anti-relapse purpose were developed. It was shown that long-term use of PT in the period of recovery was safe and reducing frequency of "+" virus relapses by 1.9 times and "-" virus relapses by 1.3.

Practical importance of obtained results. The proposed two-staged treatment course for patients with HVI (basic and anti-relapse) with differentiated approach to the selection of ethiopathogenetic treatment regimen and justified need for follow-up monitoring of those, who have recovered.

Instructions for PT usage in monotherapy have been developed, in combination with ANAD. The possibility has been shown to reduce ANAD dosage by 20% at the expense of comprehensive ethiopathogenetic action of PT.

Implementation of study results. The results of work were integrated into the diagnostic and treatment process in the intensive care, detoxication and neuroinfections medical units of L.V. Gromashevskiy Institute of Epidemiology and INFEKTIOUS DISEASES of the Academy of Medical Sciences of Ukraine. According to dissertation materials, the Ukrainian Center of Scientific Information and Patent-Licensing Work for the Ministry of Healthcare of Ukraine issued information letter — "Methodology of Use of Proteflazid in Treating Patients with Herpes Virus Infection" (No. 42-2004).

Author's personal contribution. The author independently planned the study, carried out information and patent search, and analyzed the scientific literature. She established purpose and objectives of the study. She personally carried out clinical selections of patients, dynamic observations and treatment of patients with HVI, gathered biological material for clinical, immunological and virological studies. She independently carried out statistical processing of material, analysis and generalization of obtained results.

Work products approbation. The materials of paper were represented and discussed at the scientific practical conference "Topical Infectology Questions" (Kyiv, 2003), international scientific practical conference "Topical Issues of Hospital Medicine" (Sebastopol, 2004), at the meeting of Kyiv City and Regional Society of Infectiologists (Kyiv, 2004), scientific practical conference devoted to 250th anniversary of the Main Military Clinical Hospital (Kyiv, 2005).

Publications. Based on dissertation topic 14 papers are published, 5 of which are magazines recommended by the Supreme Certifying Commission of Ukraine for publication of thesis research materials, methodological recommendations, 6 innovations.

Scope and structure of report. The report is represented on 89 pages and consists of introduction, literature review, and 2 chapters of personal studies, analysis and discussion of the obtained results, conclusions, practical recommendations, and references (235 sources, 85 of which are foreign sources).

CHAPTER 1

PRESSING ISSUES OF TREATMENT OF HERPES VIRUS INFECTIONS

HVI is a group of Infektious Diseases caused by structurally homogeneous group of viruses that belong to Herpesviridae family [18]. This family includes more than 100 representatives, of which HSV1 and 2, Varicella Zoster Virus (VZV), CMV, EBV, human herpes virus of type 6 (HHV6), human herpes virus of type 7 (HHV7), human herpes virus of type 8 (HHV8) are the most human-pathogenic [6, 44, 135].

It was established on the basis of numerous studies that from 65 to 90% of world population were infected with one or several HV types [114, 137]. 30-50% of herpes-infected patients are experiencing relapses during 2-3 years; chronic course of disease with relapses is experienced in different countries from 2 to 12% of people [7, 18, 44, 134]. 98 mln cases of labial herpes, 9 mln cases of Herpes genitalis with relapses, over 5000 cases of herpes encephalitis and near 50000 of ophthalmic herpes are reported in USA annually [135, 148, 190, 200, 214]. HVI rank 2nd (16%) after influenza (36%) as a cause of death owing to viral infections [6, 54, 67, 79, 114]. According to global review of HV studies, contamination and disease incidence grows annually [35, 67, 79, 114]. The most important reasons of such unfavorable dynamics include increasing number of persons with immunological disorders, chronic diseases in population structure, undesirable influence of urbanization and range of ecological factors on the humanity, emergence of acyclovir-proof forms, HV mutants. [144, 153, 205, 219].

1.2. Main principles of treatment of patients with herpes virus infections

HVI therapy belongs to the most complex and multicomponent in infectology and pharmacology [60, 134, 140, 219]. This is due to that to date there is no single drug and treatment regimen, which could be sufficiently efficient against all viruses of this family enabling to approach reliable treatment outcomes, avoid complications and relapses.

According to foreign investigators [162, 168, 219], the number of potential patients requiring for prophylaxis and treatment of HVI makes 5-8% in the developed countries and up to 15% in under-developed countries versus overall population [67, 97, 134, 168]. As for the present, the indications for treatment of herpes virus diseases [97, 134] are: 1) probability of activation of latent herpesviruses in human bodies (HIV-infected, TPL patients, cancer and diabetes

patients) [218]; 2) acute or relapsing HV disease, probable contamination of pregnant woman, fetus, damage of nervous system and internal body parts [39, 124, 157]. In such cases drugs may be indicated both for treatment and prophylaxis purpose, even when there is no direct laboratory confirmation of virus reactivation, but danger to patient's life exists, or diagnosis is established in clinics.

4 groups of anti-viral drugs are used in treating HVI: 1) chemotherapeutical agents; 2) IFN; 3) IFN inductors; 4) immunomodulators [67, 97, 134].

Chemotherapeutical agents belong to the most studied and widely used drugs in treating HVI [97, 162, 179, 219]. The use of chemical anti-viral drugs enabled reduction of case mortality of HV damages for nervous system from 80-100% to 50%, and in comprehensive therapy — up to 2-5% [60, 97, 191, 195]. Modern anti-viral chemotherapeutical agents, in view of HVI pathogenesis, according to some authors' opinion [134], must simultaneously possess hardly compatible properties: 1) high bioavailability; 2) specificity of anti-viral action; 3) absence of carcinogenicity; 4) ability to cooperate only with intracellular inclusion-targets (virions) without damaging healthy body cells; dose-dependent relationship; 5) properly excreted from the body and no general toxical properties. However, in practice, the most important of all these properties are anti-viral selectivity of drug action and absent or minimal toxicity [201]. According to chemical structure all anti-viral drugs fall into several groups: acyclic equivalents of nucleosides (a-, val-, gan-, fam-, penciclovir), pyrimidine nucleoside equivalents (idoxuridine, trifluormidine, brivudine, sorivudine), acyclic nucleoside phosphonates (cidofovir, adefovir), carbocyclic nucleoside equivalents (lobukavir), pyrophosphate equivalents (foscarnet) [97, 162, 179, 215]. In Ukraine only acyclovir, valciclovir, ganciclovir and idoxuridine in eyedrops form are registered and permitted for clinical use [97].

As other anti-viral drugs, AC is targeted at virus enzymes resulting in interruption of propagation thereof [97, 134, 162, 195, 215]. Their anti-viral activity in order of descending is the following: HSV1, HSV2, VZV, EBV, HHV6, HHV7, HHV8, CMV, and makes 75-90% for HSV infections; 60-80% for VZV infections; 30-70% for CMV [91, 126]. The literature sources contain data on possibility of undertaking long-term suppressive AC therapy (6-12 months) in patients with frequent relapses or patients against the background of immunodeficient state. However, this information raises doubts, as AC possesses poor bioavailability (15-20%) when taken per os. The sufficient concentrations of AC in blood and CSF are approachable only under condition of intravenous administration, and long-term random courses of drug administration with

predominantly intravenous administration of drug may result in formation of HV resistant strains (from 4.7% to 25% cases) [38, 67, 97, 189]. Acyclovir-proof strains are most often encountered in HIV-positive patients [38, 189].

Some investigators [222] took notice of relapses developing after dechallenge of AC and other chemical anti-viral drugs. Fast reduction of drug concentration in blood may result in viruses reactivation within up to 10 days after drug dechallenge [222]. Such early relapses constitute the largest problem for patients with HV neuroinfections, since each following reactivation of viruses leads to deterioration of the condition and increase of unavoidable morphological modifications in brain tissues. Nevertheless, despite pharmacokinetic disadvantages, AC is still considered to be the gold standard of anti-viral therapy [61, 62, 97, 126, 162, 196, 219].

Valciclovir is L-valine ether AC, which has higher bioavailability (70-80%) enabling reduction of dosage frequency from 5 to 1-2 times a day. It is shown that according to clinical efficacy in treating acute and prophylaxis of relapsing HVI this drug exceeds AC by 25-40% [97]. To date, it is a basic chemical anti-viral drug widely used for treatment both in acute period and when carrying out extended suppressive therapy [81, 184]. For instance, according to Peitil R. (1999), a single administration of drug 500 mg daily dosage during 16-48 weeks made a significant suppressive effect preventing or constraining 69-85% of HG relapses. However, extensive use of this drug is limited by its high cost and probable development of toxic hepatitis and nephritis due to long-term administration.

Ganciclovir — acyclic nucleoside, a synthetic equivalent of guanine, which inhibits replication of HV [134]. GC is more effective against CMV, which has no thymidine kinase gene; but despite a wide range of viruses susceptible hereto, this drug has a high gemmo- and hepatotoxicity that limits its use [91, 97]. It is due to that GC, as comparing with AC, is the best possible substrate for cellular thymidine kinase and is phosphorylated by them. Owing to this fact it is included in pool of phosphorylated nucleosides in non-infected cells. This process flow the most intensively in cells, which quickly divides, for example, in bone marrow cells. Its gemmotoxicity is connected with this process. The experimental studies demonstrated that GC can also cause chromosome mutations in mammalian cells and inhibit spermatogenesis in males and reproductive function in females. In this regard, patients are recommended to use contraceptive agents during treatment and within 90 days upon its completion. The drug must not also be administered without important indications to newborns, babies under 2 years, boys under 9 years and pregnant women [81, 97].

Another one problem of using this drug is the development of CMV resistance to GC (up to 38% in HIV-infected patients) [38]. For resistance prevention, the combined use of anti-viral drugs with different actions (foscarnet, cidofovir, vidarabin) is recommended, however, following such therapy their toxicity is significantly growing.

Vidarabin (Ara A), foscarnet, cidofovir, adefovir, trifluridine, sorivudine, brivudine are drugs not registered in Ukraine. Abroad this group of drugs is used, primarily, only for treatment of diseases caused by AC-proof strains, since wider indication is limited by their high toxicity [91, 177, 189].

Consequently, instead of material advances in the field of anti-viral therapy and the sufficient variety of etiotropic drugs, treatment of HVI chronic forms with relapses represents a challenging problem to date, as HVI monotherapy with chemical anti-viral drugs does not provide any steady therapeutical effect. On this basis and following the results of HVI pathogenesis study, investigators from around the globe arrived at the need of complex use of anti-herpetic drugs and immunobiological agents (interferons, IFN inducing agents, immunomodulators and immunoglobulins) [80, 81].

Immunotherapy, so as IFN therapy to date, is the main direction of pathogenetic approach to treatment of HVI [81]. For HVI IFN therapy interferons and their inducing agents are used.

Among IFN in HVI therapy those IFN are mainly used, which are developed by genetic engineering, various α-2-IFN subtypes (Intron-A, roferon, berofor, egiferon, feron, reaferon, realdiron) [81, 96]. Despite pathogenetic justification of using IFN, this therapy still has some side and undesirable effects of systemic nature. For example, according to some authors [81, 96, 145], undesirable effects at IFN therapy are encountered in 90% of cases. The most often is flu-like syndrome (75-90%), cytolytic crisis with increasing transaminase level by 5-20 times (10-45%), intrahepatic cholestasis (12-15%), dyspeptic disorders (14-18%), thrombocytopenia and leucopenia (9-17%). IFN are also capable to intensify asthenic syndrome phenomena, induce convulsions, dizziness, paresthesias, violate cognitive functions (33%), intensify depressive syndrome right up to attempted suicides [96, 145]. In addition, IFN are not recommended for use by patients with serious damages of nervous system and active autoimmune processes, which limit their use in patients with neuroinfections, especially in chronic course with relapses. Also, another one challenging issue of IFN therapy is represented by different sensitivity of HV to IFN action [97]. HSV1 and HSV2 are highly-sensitive. The question remains open concerning sensitivity of CMV, EBV, HHV6,

HHV7, HHV8 to IFN, since any exact experimental data and confirmations for its efficacy is absent [97].

The use of interferon inducing agents and immunomodulators [68, 73, 77, 113, 119, 144] are of great importance in comprehensive therapy, as endogenic IFN inducing agents have a range of advantages against recombinant IFN: 1) active in relation to a wide range of DNA and RNA viruses; 2) possess no antigenic power; 3) cause no hyperinterferonemia; 4) induce α- and γ-IFN synthesis; 5) IFN production is controlled by the body. IFN inducing agents are recommended for use both in acute phase along with comprehensive therapy with anti-viral drugs and in the form of monotherapy during intercurrent period.

The group of immunomodulators is big enough, so as IFN inducing agents. The action of immunomodulators in most cases is associated with their ability to influence on the activity of intracellular AMP / cAMP. It has been proved that taking part in almost all immune responses these drugs may increase creation of antibodies, promote phagocytosis, strengthen cytotoxic activity of lymphocytes, inhibit delayed-type hypersensitivity, and make impact on the processes of immunological memory realization [77, 144]. Beside immunomodulatory action, a range of drugs can trigger interferon systems, which make it possible to consider them as IFN inducing agents [73, 144]. In HVI therapy the most frequently used are cicloferon, neovir, amixin, amizonum, polyoxidonium, immunofan, larifan, poludan, galavit, erbisol [73, 77, 119, 144].

Despite the wide integration of IFN inducing agents and immunomodulators in practice, polemics is still being carried on concerning reasonability of their use for treatment of HVI. For example, some authors [134] deem that immunomodulatory action is nonspecific and not studied to the full degree, as well as the best possible indications are identified according to timing and duration of using immunomodulators at the various stages of the infection process. So, this issue still remains understudied and requiring scientific improvement.

Among approbated antiherpetic agents, antiherpetic vaccine holds a special place, reasonability of which use has currently raised the material polemics. While studying action of this vaccine [90, 187], it was proved that vaccination promotes a cellular component of immune system without significant influence on the humoral immunity. Vaccination was indicated due to the frequent relapses of eye, skin and mucosa herpes [7, 90, 187]. According to authors, such treatment policy ensures the pronounced immune stimulating effect and enables avoiding complications. However, despite proved therapeutical efficacy, the disputes concerning reasonability of vaccine therapy originated in the scientific community, as with the

immunomodulatory therapy [134]. They were grounded on non-sufficient properties of vaccine and probability of autoimmune reaction development. According to the group of scientists [134], all vaccines created before now can promote producing antibodies, but not able to promote producing and activity of killer cells being the most important for antiherpetic immunity. In addition, information was published about that antiherpetic vaccine therapy results in overstimulation of antibody response, following which vaccines may suffer from systemic autoimmune diseases, usually demyelinating diseases of CNS [134]. In USA only live attenuated vaccine against VZV is used, which possesses 7-90% efficacy [226]; a few experimental vaccines against CMV, EBV are at the development stage [187].

When treating HVI, human normal, non-specific multivalent and specific immunoglobulins are used. Specific immunoglobulins have been more recently preferred for passive immunization. It was encouraged by the emergence of series of immunobiological drugs against HSV, CMV, EBV [81, 140] on pharmacological market of Ukraine. All immunoglobulins are reasonable for use at the early stages for HVI acute forms or relapses, especially at CNS damage, or for the purpose of preventing infection [60, 81]. According to some authors [60, 61, 140], such usage of immunoglobulins provides a pronounced clinical effect: improves the course and reduce duration of disease, prevent the development of undesirable effects and signs.

The foregoing summary reflects, on the one side, variety of drugs and sufficient studying of HVI pharmacotherapy issue, and absence of unified treatment regimens capable to ensure prevention of recurrent HVI relapses, on the other side. In this regard, treatment regimens are still being improved [171, 196, 198, 199, 230, 231].

As has been noted above, now the comprehensive HVI therapy patterns are used, which include several drugs with different actions. But in some cases even a complex action appears to be ineffective; in addition, some difficulties may occur with pharmacological combination and drugs administration sequence.

The solution of problem can be in Proteflazid (“Ecopharm”, Ukraine), which possesses anti-viral, interferon inducing and immunomodulatory effects at the same time [5, 106]. Proteflazid features a liquid ethanolic extract of wild cereals — Deshampsia Caespitosa L. and Calamagrotis Epigeios L., which bioactive substances are flavonoids. One drop of drug contains 2-5 mcg of flavonoid glycosides. The drug possesses anti-viral action following inhibition of virus-specific enzymes of thymidine kinase and DNA polymerase in virus-infected cells,

which results in decrease of ability or complete blockage of virus proteins replication [5, 106, 109].

According to preclinical and clinical studies PT possesses a broad spectrum of action against herpes simplex viruses of types 1, 2, 4, 5, 6 and 8, picornaviruses, papovaviruses, hepadnaviruses, rhinoviruses, reoviruses, paramyxoviruses, adenoviridae [4, 24, 42, 89, 109]. Publications exist devoted to clinical efficacy f PT in treating chronic chlamydial, mycoplasmal, fungal infections [21, 66, 111, 131]. PT induces the synthesis of endogenic α- and γ-IFN in high titres in as little as 3 hours after the drug administration, which enables ranging it in group of interferon inducing agents [5, 42, 89]. It was noted experimentally and practically that drug has a range of positive properties: apoptosis-modulating; cerebral protecting (normalizes excitation and inhibition processes in central NS, boosts mental and physical work capacity); antioxidative; detoxicative (deactivates alcohol and its aldehydes, narcotic and ammonia-containing substances) [85, 106, 131]. The drug belongs to low-hazardous substances having no mutagenic and carcinogenic actions, which makes it safe for long-term use both in children and adults [4, 85, 89, 110].

When administered per os, PT is partially absorbed in stomach, and in bowel to a greater extent. A little quantity of drug is metabolized during the first passing through liver, but its main part is allocated among organs and tissues, penetrating virus-infected cells [106].

Therefore, on the basis of abovementioned properties, PT can be used in HVI therapy both in the acute phase and during convalescence period for anti-relapsing purpose. There is no data in literatures available, which could characterize therapeutical, immunomodulatory, interferon inducing and anti-relapsing activity of PT in patients with HVI, for which reason further studying of these issues is desirable.

For successful treatment of patients with HVI it is necessary to combine specific etiotropic with pathogenetic and symptomatic therapies. While carrying out pathogenetic treatment of HVI, it could be reasonable to use not only traditional medications (vascular, inflammatory, rheocorrecting), but also efferent treatment methods (blood ultraviolet irradiation, plasmaphairesis, blood laser irradiation), which may materially potentiate ethiopathogenetic treatment [22, 74, 88, 117, 146].

The results of literature analysis speak for that to date HVI represents a serious medico-social problem. It is associated with a significant contamination of

population globally with HV (up to 90-100%), excess of incidence rate, complexity of pathogenesis and severity of HVI course. Clinico-neurological manifestations of HV damage to NS are multi-faceted, but in literature the examples of acute forms of encephalitis, meningitis are more often provided, and data on other neurological cases observed both during acute and chronic disease course with relapses due to monoviral and associated HVI are almost absent. Our opinion is that the issue of immunological disorders in the course of different clinical options of HV neuroinfections is still underserved. The issues of immunological indicators monitoring throughout disease against the treatment also remains unsolved. However, it is obvious that for efficient treatment, HVI therapy regimens must include drugs with immunomodulatory, interferon inducing and rheocorrective actions. Despite the creation of specific anti-viral drugs, HVI therapy is still topical for both infectiologists and other profile doctors. It is associated with that no treatment regimen can ensure a complete relief of body from viruses or prevent relapsing or disease progression. HVI therapy is expensive, and in some cases toxic, which significantly restricts its extensive use. In this regard, the search for new drugs and reasonable combinations thereof, capable to increase efficacy, safety and availability of HVI therapy, continues. Thus, it can be a prospective treatment option to include anti-viral PT in comprehensive HVI therapy regimens.

CHAPTER 2 MATERIALS AND STUDY METHODS

2.1. Characteristic of examined patients

The study subjects were HVI-infected patients, who were receiving medical treatment in L.V. Gromashevskiy Institute of Epidemiology and Infektious Diseases, in neuroinfections, intensive care, and detoxication medical units. From the year 2002 to 2005 236 subjects were examined, in particular, 79 males, 157 females, in the age from 18 to 66 years (the average age was 34.6 ± 12.6). In Table 2.1 the subjects are listed divided by age and sex. As it is seen from the table, from the point of age, persons of juvenile — 104 (44.07%) and ripe age — 108 (43.22%) prevailed.

Table 2.1.

Breakdown of subjects by age and sex

Age	Male		Female		Total	
	Abs.	%	Abs.	%	Abs.	%
18-19	18	22.78	17	10.83	35	14.83
20-29	21	26.58	48	30.57	69	29.24
30-39	14	17.72	42	26.75	56	23.73
40-49	11	13.92	35	22.29	46	19.49
50-59	14	17.72	7	4.46	21	8.90
60-69	1	1.27	8	5.10	9	3,81
Total	79	33.47	157	66.53	236	100.00

The diagnosis was established on the basis of medical history data, physical examination of physical and neurological statuses of subjects, results of virological (PCR, ELISA) and instrumental study methods (MRT of brain and spinal marrow, EEG, USDG). Etiologic factor was determined by way of detecting markers of HV replicative activity in blood and CSF.

The diagnosis was clinically formulated with regard to the nature of damage to central and peripheral NS and etiologic factor according to classification of HV damages to NS [62]. Based on combination of infectious, cerebral, cerebrospinal fluid, focal symptoms and brain MRT data we distinguished the following forms of HV damages to NS: meningoencephalitis, meningoencerebritis — in 150 (63,6 ± 3,1)% patients, disseminated encephalomyelitis — in 43 (18.2 ± 2.5)%, encephalomyelopolyradiculoneuritis — in 43 (18.2 ± 2.5)%. Among patients diagnosed with MC, ME and DEM there were twofold more females than males (72.6% and 74.4%, accordingly). The inverse trend was observed among patients with EMPR (62.8% of males). The average age of patients with such clinical forms

as ME and DEM was almost similar (32-36 years), unlike patients with EMPR, whose average age was older and constituted 41.2 ± 13.7 years (|r| d0.22; p=0.005).

The severity of conditions of patients was assessed based on the following criteria [51]:

- pronouncement of neurological symptomatology (hemispheric and craniobasal symptoms);
- level of consciousness according to Glasgow scale;
- degree of vital functions disorders;
- pronouncement of somatic disorders;
- nature and pronouncement of laboratory changes.

The acute course included cases with duration of disease up to 3 months; subacute — from 3 to 6 months; chronic — more than 6 months [141, 124]. According to these criteria, chronic course of disease with relapses was observed in 131 (55.5 ± 3.2)% patients, subacute — in 76 (32.2 ± 3.1)%, acute — in 29 (12.3 ± 2.1)% patients. Disease duration (from the moment of first symptoms to hospitalization of patients) varied from several days to 20 years (3.5 years at the average). Duration of disease up to 1 year was observed in 70 (29.7%) cases, up to 5 years — in 114 (48.3%), up to 10 years — in 43 (18.2%), up to 15 years — in 7 (3.0%), over 15 years — in 2 (0.8%) cases. The majority of patients (75.4 ± 2.8)% experienced moderate severity form of disease, 58 (24.6 ± 2.8)% — severe form. We registered no mild forms of disease.

In 136 (57.6 ± 3.2)% patients results of simultaneous blood and CSF tests did not coincide either by serologic profile or etiopathogenesis type. For example, HV DNA by PCR method was detected in 55 (23.3 ± 2.8)% patients (in 29 (12.3 ± 2.1)% cases — in blood, in 26 (11.0 ± 2.0)% — in CSF). Specific IgM were detected by ELISA in 128 (54,2 ± 3.3)% subjects (in 125 (53.0 ± 3.3)% cases — in blood, and in 3 (1.3 ± 0.7)% — in CSF). Specific IgM and HV DNA in blood were detected against the high level of IgG, which evidenced reactivation of persisting HVI. The increased titres (>1:20) of specific IgG in CSF were determined in 116 (49.2 ± 3.3)% cases, among which in 53 (22.5 ± 2.7)% — up to more than one HV type. The signs of HSV replicative activity were the most frequently (45.5 ± 4.2)% determined in CSF. The markers of CMV (28.3 ± 3.8)%, EBV (15.9 ± 3.0)%, HHV6 (7.6 ± 2.2)% and HHV8 (2.8 ± 1.4)% replications were somewhat less frequently determined, which correlates with other authors' data. Etiological structures of HV neuroinfections are listed in Table 2.2.

Table 2.2.

Etiological structure of herpesviral damages of nervous system

Virus / Viruses type	Clinical form							
	MC, ME n=150		DEM n=43		EMPR n=43		Total, n=236	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
HSV1/2	24	16.0	7	16.3	15	34.9	46	19.5
CMV	11	7.3	5	11.6	3	9.4	19	8.1
EBV	26	17,3	4	9.3	1	3.2	31	13.1
HSV1/2 + CMV	40	26.7	5	11.6	9	20.9	54	22.9
HSV1/2 + CMV + EBV	19	12.7	10	23.3	7	16.3	36	15.3
HSV1/2 + EBV	16	10.7	2	4.7	1	2.3	19	8.1
HSV1/2 + HHV6	5	3.3	2	4.7	—	—	7	3.0
CMV + EBV	2	1.3	—	—	3	7.0	5	1.7
HSV1/2 + CMV + HHV6	1	0.7	3	7.0	—	—	4	16.9
HSV1/2 + HHV6 + HHV8	2	1.3	2	4.7	—	—	4	1.7
HSV1/2 + CMV + EBV + HHV6	2	1.3	—	—	1	2.3	3	1.3
HSV1/2 + VZV	1	0.7	1	2.3	1	2.3	3	1.3
HSV1/2 + EBV + HHV6	1	0.7	—	—	1	2.3	2	0.8
HSV1/2 + CMV + HHV6 + HHV8	—	—	1	2.3	—	—	1	0.4
HSV1/2 + CMV + VZV	—	—	—	—	1	2.3	1	0.4
EBV + HHV6	—	—	1	2.3	—	—	1	0.4

As can be seen in the table, active mono-HV infection was detected in 95 (40.3 ± 3.3)% patients, in which structure HSV1/2 was the most frequently (19.5%), and EBV (13.1%) and CMV (8.1%) — less frequently encountered. In 141 (59.7%) patient, within one and/or two biological media, DNA fragments and/or diagnostic titres of specific bodies of IgM and IgG types up to several HV types were determined, on which basis we suggested existence of mixed HVI in this group subjects.

Totally, we distinguished 13 types of associations, among which a significant prevalence of three combinations of viruses was noted: HSV+CMV (22.9%), HSV+CMV+EBV (15.3%), HSV+EBV (8.1%). Inclusions in associations of clinically and therapeutically understudied HHV6 (18 cases) and HHV8 (5 cases)

HV types were detected in associations along with the main HV types (HSV, CMV, EBV) (see Fig. 2.1).

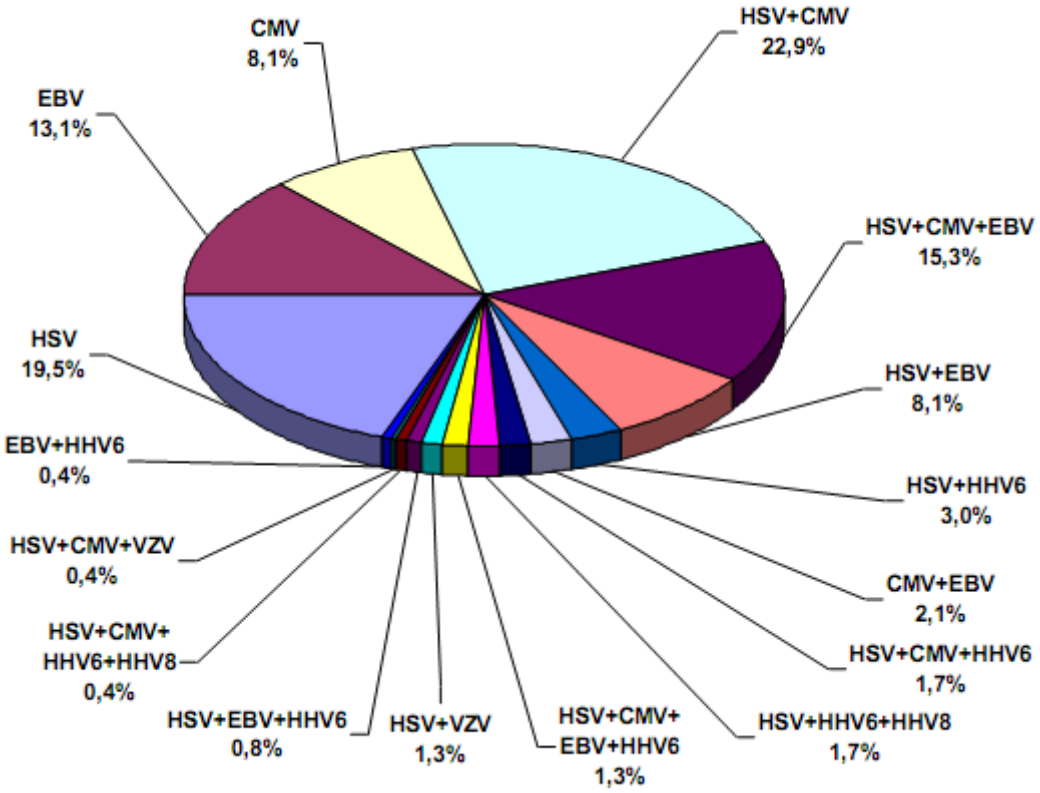

Fig. 2.1 Frequency (%) of detection of various herpesviruses types.

The subjects with the acute onset of disease experienced cases of monoherpesviral (51,7 ± 9.4)% and mixed HVI (48,3 ± 9.4)% with the same frequency. Mixed HVI was more often (48.3 ± 9.4)% versus monoviral (44.7 ± 5.7)% detected in subjects with subacute disease course. More significant difference in these indicators is observed in subjects with the chronic disease course, where frequency of mixed HVI detection is twofold exceeding (64.9 ± 4.2)% monoviral (35.1 ± 4.2)% (see Fig. 2.2).

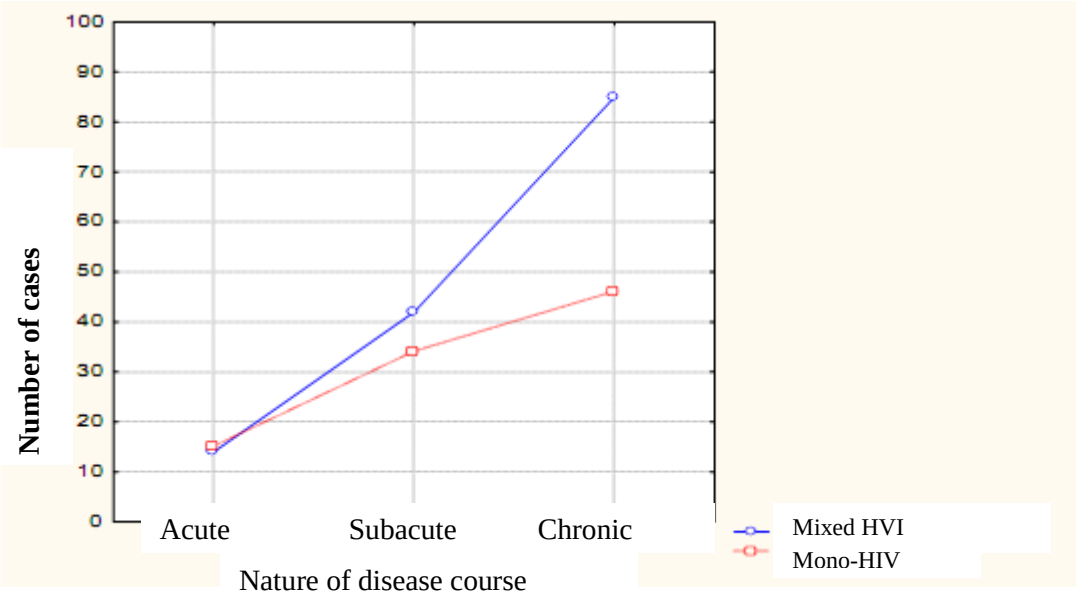

Fig. 2.1. Frequency of detection of mono- and mixed herpesviral infections depending on the nature of disease course.

Despite the variety of HVI clinical manifestations, each etiological type has its own pathognomonic neurological symptom. Combination and pronouncement of neurological syndromes data reflects the level and depth of NS damage and determines HVI clinical form. When observing subjects, it was discovered that along with the signs of central and peripheral NS damage, the signs of internal parts involvement in pathological process was also seen. Key role in visceral pathology development pathogenesis in subjects with monoviral infection is played by EBV, CMV, with mixed HVI — by HSV + CMV + EBV combination.

The main neurological symptoms and syndromes diagnosed for HVI subjects are listed in Table 2.3.

Table 2.3

Main neurological symptoms and syndromes in subjects with herpesviral infection

Syndromes / symptoms		Meningoencephalitis, meningoencerebritis, n = 150		Disseminated encephalomyelitis, n=43		Encephalomyelopolyradiculoneuritis, n=43		Total, n=236	
		Abs.	%	Abs.	%	Abs.	%	Abs.	%
Asthenic syndrome		150	100	43	100	43	100	236	100
Cerebral symptoms	Headache	150	100	41	95.4	40	93.0	231	97.9
	Hyperacusia	30	20	4	9.3	4	9.3	38	16.1
	Photophobia	30	20	4	9.3	4	9.3	38	16.1
Impairment of consciousness	Clouding of consciousness	15	10	3	7.0	4	9.3	22	9.3
	Semicoma	4	2.7	—	—	—	—	4	1.7
	Coma	2	1.3	—	—	—	—	2	0.8
Motor defects	Hemiparesis	65	43.3	15	34.9	7	16.3	87	36.9
	Paraparesis	8	5.3	5	11.6	15	34.9	28	11.9
	Tetraparesis	1	0.6	11	25.6	12	27.9	24	10.2
Sensuous defects	Hypesthesia	29	19.3	16	37.2	20	46.5	65	27.5
	Hyperesthesia	68	45.3	27	62.8	24	55.8	119	50.4
	Paresthesia	157	84.7	37	86.0	39	90.7	203	86.0
Akinetic-rigid syndrome		—	—	2	4.7	2	4.7	2	0.8
Little brain disorders		56	37.3	34	79.1	28	65.1	118	50.0

Continuation of Table 3.3

Syndromes / symptoms		Meningoencephalitis, meningoencerebritis, n = 150		Disseminated encephalomyelitis, n=43		Encephalomyelopolyradiculoneuritis, n=43		Total, n=236	
		Abs.	%	Abs.	%	Abs.	%	Abs.	%
Cerebral nerves dysfunction (III-VII, IX, X, XII)		114	76.0	38	88.4	26	60.5	178	75.4
Epileptiform syndrome	Focal convulsions	9	6.0	8	18.6	1	2.3	18	7.6
	Generalized convulsions	4	2.7	5	11.6	1	2.3	10	4.2
Bulbar disorders		3	2.0	6	14.0	8	18.6	17	7.6
Psychopathological syndrome		95	63.3	37	86.0	38	88.4	170	72.0
Pelvic organs dysfunction		19	12.7	29	67.4	26	60.5	73	30.9
Cognitive disorders		56	37.3	37	86.1	20	46.5	103	43.6
Cortical disorders	Speech disorders	8	5.3	14	32.6	13	30.2	35	14.8
	Writing disorders	7	4.7	11	25.6	9	20.9	27	11.4
Liquor hypertensive syndrome		93	62.0	28	65.1	17	39.5	138	58.5
Meningeal syndrome		15	10.0	4	9.3	3	7.3	22	9.3
Vegetative disorders		109	72.7	32	74.	41	95.4	182	77.1
Neuroendocrinal syndrome		15	21.4	8	18.6	8	18.6	31	13.1

2.2. Characteristic of study drug and treatment methods

Proteflazid is an antiviral drug (ATC J05 AX), made In Ukraine and approved by order of the Ministry of Healthcare of Ukraine dd. February 14, 2001 No. 56. Registration certificate No. P.02.01/02777 [106]. PT possesses an antiviral, immunomodulatory, interferon inducing, cerebral protecting, and anti-oxidant actions [109].

At the initial hospital or outpatient treatment PT was administered during 2 months in the following dosage: 10 drops three times a day. Further, subjects with EBV, CMV or mixed HVI, where diseases lasted for more than 3 years in severe of chronic course with relapses (relapses rate over 2 times a year), continued taking PT for anti-relapsing purpose without intervals for a year (within 6 months — 10 drops 3 times a day, afterwards 8 drops 3 times a day — within 3 months, then by 5 drops 3 times a day — within 3 months). In this period they were followed-up each 2-3 months with virological and serological profiles check-up. The patients without the aforementioned signs were taking the drug for anti-relapsing purpose during 6 months (up to 3 months — by 10 drops 3 times a day, 1 month — by 8 drops 3 times a day and 2 months — 5 drops 3 times a day).

After the drug administration (in order to assess efficacy and control every potentially adverse effect) the patients were monitored according their physical and neurological profiles, and the dynamic control was carried out for laboratory indicators. AE was deemed any medical event in the form of complaints, symptomatology, laboratory deviations or disease, which were originated or intensified versus initial state, during the clinical study with study drug regardless causation. The following were deemed as AE: 1) adverse medical reactions; 2) other medical events (variations of laboratory indicators, traumas); 3) reactions at overdosage, improper administration, dechallenge, toxicity or absence of the expected pharmacological effect.

2.3. Study design

The study was conducted based on the provisions of Helsinki Declaration of the World Medical Association and ICH-GCP Guidelines, voluntary participation, provision of information to subjects on nature of the future study.

2.3.1. Subjects enrollment and discontinuation criteria

Subjects were enrolled to the treatment and examination regimens according to the specially developed selection criteria.

Enrollment criteria were the following: 1) existence of pathological neurological symptomatology typical for MC, ME, DEM, EMPR; 2) etiological confirmation of disease with the markers of HV replicative activity by PCR and/or ELISA methods in blood and/or liquor; 3) patient's age from 18 to 70 years; 4) voluntary consent of the subjects to take part in the study.

Discontinuation criteria: 1) concomitant diseases capable to influence on the proper assessment of the subject's immune status (HIV-infection, insulin dependent diabetes mellitus, hematological diseases, malignant tumors, liver and kidneys impairments at the stage of decompensation); 2) using immunosuppressive therapy, interferons, interferon inducing agents, specific immunoglobulins by subjects before hospitalization.

2.3.2. Principles and algorithm of subjects grouping

For determination of purpose and objectives, we divided the subjects in the relevant groups: group I — 36 subjects (ethiopathogenetic therapy was based on PT administration according to developed pattern); control group II — 77 subjects (ethiopathogenetic therapy was based on ANAD administration). Subjects enrollment to basic (I) and control (II) groups was carried out simultaneously by the principle of block randomization. When choosing treatment regimen and administering ANAD in the study group of subjects, the following criteria were characteristic: 1) detection of viruses DNA in CSF or blood by PCR method; 2) acute onset and severe course of the disease; 3) expansion and depth of damage and speed of neurological symptomatology growth (cortical, subcortical and stem structures impairment, peripheral nervous system damage of progressive type); 4) existence of life-threatening complication on the side of NS (brain edema/swelling, bulbar, paroxysmal, hydrocephalus syndromes); 5) existence of numerous foci of demyelination or destruction in brain and spinal marrow according to MRT data. The existence of first criterion in combination with anyone of the 5 was an absolute indication for inclusion of ANAD into the treatment regimen.

According to these criteria, AC or GC was included in the treatment regimen of group II subjects depending on etiological factor. AC was administered to group II subjects intravenously, dropwise, calculated as 20-25 ml/kg of subject's body weight during 10-14 days, GC (cymeven) — 10 mg/kg of weight during 10-14 days. Valtrex was also used calculated as 10 mg/kg of subject's body weight during 10-14 days. The immunosupportive (normal human immunoglobulin, specific immunoglobulins with the increased antibodies titres against HSV, CMV, EBV) and interferon supportive (α^2-interferon drugs and their inducing agents) therapy was sometimes additionally used to group II subjects.

The criteria of administration of therapy without ANAD and formation of group I of subjects were: 1) detection of only increased titres of IgM, IgG class specific antibodies to HV in biological media; 2) mild or moderate disease course; 3) subacute or chronic relapsing disease; 4) prevalence in neurological clinics of monosyndrome or the condition without tendency to disease progression; 5) absence of life-threatening states; 6) presence of severe concomitant pathologies at the stage of sub compensation on the side of liver, kidneys, drug disease, allergic responses in the past medical history; 7) inefficiency of the forgoing antiviral therapy courses.

Vasoactive agents (vinpocetine, pentoxifylline, lysine-aescinat), hormones (dexamethasone), nonsteroidal antiinflammatory drug (diclofenac), oncology drug (magnesium sulfate, rheosorbilact), anti-oxidant and vitamin agents, amino acids (glutargin, ascorbic acid, thiamine bromide, pyridoxine hydrochloridum, nicotinic acid) were used in all control groups in the capacity of pathogenetic-symptomatic therapy in therapeutic dosages.

The subjects were grouped according to the above listed enrollment and discontinuation and selection criteria. The groups were not statistically differing ($P<0.05$) according to sex (χ^2 of Pearson = 0.86; MPχ^2=0.86) and age (Median test=0.055) indicators.

Owing to the complexity of subjects etiological structure, the groups had statistically significant differences ($P<0.05$) according to frequency of some viral mixture encountered. To overcome this factor, we have enlarged some etiological groups. All groups included the patients both with mixed and monoviral HVI. The viruses with different allelically determined sensitivities to ANAD and various biological properties were observed within the groups almost at the same rate, which at the first analysis stage allowed to consider groups as being compared according the etiological factor.

2.3.3. Assessment of therapy efficacy

The therapeutical efficacies of treatment regimens were assessed by way of comparing dynamics of recession of pathological symptoms, rate of residual effects, nature of change of dynamics of antibodies DNA negative reaction and seroconversion, rate of detection and nature of AE in groups, dynamics of hemmostasiologic and immunological indicators and analysis of long-term therapy results.

In order to simplify therapy efficacy analysis we created a percentage system of assessment. This system was based on reducing pronouncement of pathological

neurological and physical symptomatology in patients after completion of the treatment course. We assessed disappearance of all pathological symptoms as an excellent result, reduction of pathological symptoms by 75% — as a good result, by 50% — satisfactory, by 25% — minor, and preservation of all symptoms — as an absence of therapeutical effect. The study was carried out according to the symptoms observed in clinical and therapeutical groups with a rate exceeding 50% and according to symptoms, which influenced on the disease forecast.

2.4. Study methods

Clinical, laboratory and instrumental diagnostics methods, as well as the modern methods of statistical processing of medical data were used for achievement of purpose and objectives of dissertation.

2.4.1. Clinical method

Clinical study was conducted in all 236 subjects immediately in the course of hospital or outpatients treatment with the following daily subjective and objecting follow-up of subjects' general state, past medical history analysis. Dispensary follow-up of subjects continued during the period of reconvalescence (up to 2 years).

Subject's physical status was assessed according to the following data:

1) therapeutical examination of subject (review, palpation, percussion, auscultation of organs and systems);
2) neurological examination according to the standard methodologies;
3) laboratory general clinical, biochemical, hemmostasiologic (5022 studies), immunological blood examination (in 93 subjects), general clinical investigation of liquor (in 187 subjects);
4) instrumental examination: MRT of brain (189 studies) and spinal marrow (25 studies); EEG (49 studies); USDG of brain vessels (48 studies); electromyography (10 studies); ECG (67 studies); ultrasound investigation of abdominal cavity organs (35 studies), heart (20 studies); SCT of chest (8 studies);
5) doctor's decisions (cardiologist, neurologist, psychiatrist, endocrinologist, neurosurgeon, gynecologist).

The general clinic, hemmostasiologic, biochemical blood examinations throughout disease were made to 170 subjects (at hospitalization with the follow-up in every 7-10 days of in-patient treatment). The general clinical CSF study was

carried out to 187 subjects during hospitalization, in 22 subjects — in the disease course. The studies carried out in the institute's clinicodiagnostic laboratory in line with the generally accepted methodologies (accreditation certificate No. PT (ПТ)-0377/04 dd. 20.12.2004 — Head of Laboratory, the Honoured Doctor of Ukraine Vasylenko L.H.) are represented in Table 2.5.

Table 2.5

Body constants under study and their methods for determination

Indices, measurement units (reference values)	Study methods
Red blood cells, 10^{12}/l (3.7–5.1 ± 10%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Determination of quantity at the permanent dilution and volume
Hemoglobin, g/l (120-160 ± 2%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Anodic method
White blood cells, 10^9/l (4.0-6.0 ± 10%) • eosinophils (0.5-5%) • lymphocytes (19-37%) • monocytes (3-11%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Quantity determination at the permanent dilution and volume
neutrophils: • segmented 47-72% • stab 1-6%	Order of the Ministry of Healthcare of the USSR No. 1175 dd. 21.10.79 Method of painting direct blood smears according to Mai-Grunwald
Thrombocytes, 10^9/l (180.8-400.0 ± 10%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Calculation at 1000 erythrocytes in smears
Erythrocytes sedimentation rate (ESR), mm/h (2-15 ± 10%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Micro-Panchenkov technique
Hematocrit, g/l (0.36-0.48 ± 3%)	Order of the Ministry of Healthcare of the USSR No. 1175 dd. 21.10.79 Centrifuge method
Total bilirubin in blood, umol/l (8.6-24.5 ± 10%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Iendrassik-Clehhorn-Hrof technique
Creatinine in blood, mmol/l (2.5-6.3 ± 8%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Popper's method (Jaffi color reaction)

Blood urea, mmol/l (44-115 ± 6%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Method of reaction with diacetyl-monoamine in the presence of ferrous ions
Alanine aminotransferase activity, umol/hl (x0.01-0.68 ± 7%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Modified method without activation by pyridoxalphosphate
Aspartate aminotransferase activity, umol/hl (x0.1-0.68 ± 7%)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Modified method without activation by pyridoxalphosphate
Prothrombin ratio, % (95-105 ± 5%)	Order of the Ministry of Healthcare of the USSR No. 960 dd. 15.10.74 Kvik-Kudryashov's method
Blood clot retraction, % 48-60 ± 1%	Order of the Ministry of Healthcare of the USSR No. 960 dd. 15.10.74 Determination of volume of serum separated during refraction
Fibrinogen, g/l (2.0-4.0 ± 10%)	Order of the Ministry of Healthcare of the USSR No. 960 dd. 15.10.74 Rutberg technique
Fibrinolytic activity, % 10-15 ± 1%	Order of the Ministry of Healthcare of the USSR No. 960 dd. 15.10.74 Kuznik, Kotovshykov technique
Clotting time, min. (8.0-12.0)	Order of the Ministry of Healthcare of the USSR No. 960 dd. 15.10.74 Lee-White, 1961
Calcium clotting time, s (90-120)	Order of the Ministry of Healthcare of the USSR No. 960 dd. 15.10.74 Beherhof, Doli, 1954
Leukocytes in CSF, cells/mcl Lymphocytes (8-10) Neutrophils (0.5-1)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Calculation of cells in smear painted according to Oppenheim per HPF (in 1 mcl)
Protein in CSF, g/l (0.22-0.33)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Method of forming ring on the boundary of liquor and nitric acid
Globulins determination in CSF + (-)	Order of the Ministry of Healthcare of the USSR No. 290 dd. 11.04.72 Pandy's test, Nonne-Apelta test with addition of carbolic acid

2.4.2. Special study methods

The disease etiology was identified by the way of detection of replicative activity markers for 7 clinically significant HV types (HSV1/2, CMV, EBV, VZV, HHV6, HHV8) by the PCR and ELISA methods. The studies were conducted in the Ukrainian Diagnostic Center (Ministry of Healthcare of Ukraine license 30028-YuR (ЮР)) and DNA Laboratory (Ministry of Healthcare of Ukraine license AB (АБ) No. 121189), laboratory of molecular biochemistry (accreditation certificate No. PT (ПТ)-0355/01) (Head of Laboratory Vasyliev I.R., Habilitation degree in Medicine) and at the division of neuroimmunology (certificate of the State Committee for Standardization and Metrology No. PT (ПТ)-0354/01) (Head of Laboratory, Lysianyi N.I., Professor) of Romodanov Neurosurgery Institute of the Academy of Medical Sciences of Ukraine according to standardized methodologies.

The study material was selected (blood, CSF) at the first encounter or during subject's hospitalization, second examination — after completion of the first therapy course (in 20-35 days) with further monitoring every 2-3 months within the first year of follow-up.

The detection of DNA viruses in liquor and blood by PCR method and/or IgM class antibodies to HV antigens by ELISA method in diagnostic titres was deemed characteristic for identification of disease etiology under condition of seroconversion in future. Also, detection of increased titres of IgG class antibodies to HV (more than 1:20) in liquor, subject to existence of relevant clinico-neurological manifestations, was considered to be diagnostic.

Immunological studies were carried out in the division of neuroimmunology (certificate of the State Committee for Standardization and Metrology No. PT (ПТ)-0354/01) of Romodanov Neurosurgery Institute of the Academy of Medical Sciences of Ukraine by the Head of Laboratory Prof. Lysianyi N.I. Cell-mediated and humoral immunity was studied in 93 subjects twice: at hospitalization (before the therapy was prescribed) and in 1 month after beginning of the drug administration — in basic group, and after completion of the therapy course (in 2-3 weeks) — in control group. The scope of immunological study included identification of qualitative indices of T- (CD3), B lymphocytes (CD20), subpopulations T-helpers/inducing agents (CD4), T-suppressors (CD8), natural killers (CD16) by the method of immunofluorescent fluoroscopy investigation with the use of set of monoclonal antibodies manufactured by Klonospektr (Russia). The functional activity of immune cells was determined according to proliferative activity indices of lymphocytes in blast-transformation reaction (BTR) with

different mitogens, cytotoxic activity of mononuclears (spontaneous and antibody-dependent), neutrophil phagocytic rate (NBT test). CIC level was identified by the method of selective precipitation of antigen-antibody complexes with 3.5 polyethyleneglycol solution, and level of autoimmune responses to neurospecific antigens (TMP, NSE) — by enzyme-immunoassay method (ELISA).

IFN activities were determined in immunological agents' quality control laboratory (Head of Laboratory, Rybalko Z.L., Habilitation degree in Medicine). IFN activity in blood serum was studied in 17 basic group subjects according to the pattern: before the drug administration, on 1^{st}, 3^{rd}, 7^{th}, 14^{th}, 21^{st}, 30^{th} and 40^{th} day of drug administration, in 7 subjects after 6 months of continuous drug administration. IFN activity in blood serum was determined by the methodology of inhibition of cytopathic effect (CPE) of vesicular stomatitis virus in the culture of calf kidney cells. Vesicular stomatitis virus (VSV) — Indiana strain was received from the museum of viruses of Ivanovsky Institute of Virology of the Russian Academy of Medical Sciences (Moscow). Infectious titer of virus in the culture of calf kidney cells made 4.0-5.0 lg TCD_{50}. VSV was cultivated in 2-day avian embryo fibroblasts culture according to the generally accepted methodology. VSV infectious titer was determined by the end-point dilution method. Virus infectious titers were determined in lg EC_{50} — end-point tenfold dilution of virus, which induced specific cells degeneration in 50% of infected wells. The cells cultures in plastic plates were processed with subjects' serum containing interferon. After 18 hours of incubation at 37°C with 5%CO_2 supply culture fluid was removed and cells were once washed with a Hank's solution and infected with VSV with 100 TCD_{50} infection multiplicity. After 30 minutes incubation in thermostat, the cells were washed and poured with RPMI-1640 media with 2% warmed fetal calf serum. The results were considered in 24-48 hours. In the capacity of IFN titer we took the figure inverse to its biggest dilution, which induced CE delay in 50% of cultures (IE (IЄ) $_{50}$/ml). IFN was typed according to acidoresistance marker. Considering that α-IFN is acid-resistant, — the type of interferon was identified as α-IFN in cases when IFN activity without and with pH variation was on the same level. If IFN activity was not identified after pH variation, then IFN type was identified as γ-interferon. If IFN activity without pH variation was in 2 sequences higher than after pH variation, then cells-produced IFN type was identified as α- and γ-IFN.

The author expresses gratitude to the head of immunological agents' quality control laboratory at L. V. Gromashevskiy Institute of Epidemiology and Infektious Diseases of the Academy of Medical Sciences of Ukraine Rybalko Z.L.

(Habilitation degree in Medicine) for the professional attention given during work on chapters “Materials and methods” and “Results of personal investigations”.

2.4.3. Statistical method

Statistical data processing was accomplished by means of computer program “Statistica”. With regard to the study objective and type of data, the following statistical methods were employed [15, 108]:

- descriptive statistics — by way of medians calculation (Me), interquartile intervals (LQ, UQ) and proportions;
- comparison of two independent groups according to the same characteristic — criterion of Mann-Whitney test, Kolmogorov-Smirnov test, Wald-Wolflowitz test, χ^2, Fisher's exact test;
- comparison of two independent groups according to the same characteristic — Wilcoxon test;
- comparison of three independent groups according to single quantitative attribute — ANOVA method by Kruskall–Wallis test, median test, χ^2 test;
- comparison of three dependent groups according to one and more characteristics — ANOVA method by Fridmen;
- simultaneous analysis of interrelation of two attributes — by the Spearman rank correlation analysis;
- simultaneous analysis of 3+ attributes — by logistic regression analysis.

Data with $P<0.05$ probability level were considered statistically significant. For the prevention of multiple comparisons problem Bonferroni adjustment was used — recalculation of p significance level for multiple comparisons. Recalculation was carried out according to the following formula: p_0/n, where p_0 — the initial given level of statistical significance, n — quantity of pairwise comparisons. The value of correlation ratio was measured within the interval from —1 to +1. Correlation force was determined with regard to correlation ratio value: $|r|\leq 0.25$ — weak correlation; $0.25 < |r| < 0.75$ — moderate correlation; $|r| \geq 0.75$ — strong correlation [108].

CHAPTER 3
ETHIOPATHOGENETIC THERAPY OF HERPES VIRUS INFECTION WITH THE USE OF PROTEFLAZID

3.1. Clinical efficacy of Proteflazid

Proteflazid was used as a main drug for 36 subjects with such clinical forms as ME (72.2%), DEM (5.6%) and EMPR (22.2%) of predominantly moderate course (88.9%), chronic with relapses (61.1%). In this group disease etiology was identified on the basis of IgM class specific antibodies in diagnostic titres. According to etiological factor, in subjects of this group combination of HSV+CMV (38.9%) viruses prevailed, less frequent other types of HV (EBV — 11.1% HSV — 16.7%) and their mixtures (HSV+CMV+EBV — 5.6%; HSV+EBV — 16.7%) were observed.

In the course of treatment we noted that overall improvement, reduction of pronouncement of asthenic syndrome in major (83.3 ± 6.3)% subjects took place on 8 ± 2.1 day of treatment, sizes of lymph nodes reduction — by 9 ± 1.7, body temperature normalization or emergence of apyrexia periods — on 10 ± 1.7 day of treatment. Feverish syndrome and lymphoadenopathy at the end of treatment were observed to persist only in 3 (8.3 ± 4.7)% subjects.

Herpetic eruptions on skin or mucosa, when admitting to hospital, were observed in 19 (52.8 ± 8.4)% subjects of this group. Against PT administration no recurrent eruptions or expansions of damage areas were detected. Skin epithelialization occurred within 7 ± 1.4 days, and mucosa — 9 ± 2.4 days.

On the side of CVS the following dynamics was present: reduction of cardialgic syndrome pronouncement, hemodynamic parameters stabilization was observed on 8 ± 4.8 day of treatment in 14 (70.0 ± 10.5)% subjects from 20 with these symptoms (arterial tension lability was persisting for a longer time, up to 11 ± 3.4 days). Vegetative dysfunction continued longer up to 9 ± 4.7 days (with prevailing parasympathetic response). Some signs of vegetative impairment preserved even after the treatment course in 22 (61.1 ± 8.2)% subjects, mainly with ME (50.0 ± 8.5)%.

On the side of digestive organs: normalization of appetite, reduction of gastralgic and dyspeptic syndromes pronouncement were observed on day 6 ± 2.0 of treatment at the average. According to physical examination, liver size was normalizing more slowly, on day 10 ± 6.4 of treatment at the average.

In neurological status, reduction of non-focal neurological symptomatology pronouncement was observed in 25 (69.4 ± 7.8)% subjects on day 8 ± 1.9 of treatment. However, despite a fast initial flow, at the end of treatment course, modified cephalgic syndrome was observed to persist (with less intensity and periodicity of seizures) in 30 (83.3 ± 6.3)% subjects, mainly with ME (63.9 ± 8.1)%. On the sensory side, reduction of algia syndrome with pain and tactile sensitivity recovery was observed on day 8 ± 3.4 of treatment in 19 (52.8 ± 8.4)% subjects. In EMPR subjects positive sensory disorders persisted for a longer time up to 12 ± 2.6 days. On the reflectory-motor side we noted tone recovery, muscle strengths in extremities and disappearance of cramps in most subjects (66.7 ± 12.6)% on day 9 ± 3.3 of treatment. Symmetry and pronouncement of tendon and periosteal reflexes was observed to recover on day 7 ± 4.0 in 17 (77.3 ± 9.1)% subjects of 22, accompanied with anisoreflexia phenomena. The signs of pyramidal insufficiency preserved after discharge from hospital too in 6 subjects, mainly with EMPR (11.1 ± 5.3)%. On CN side, a sharp recession of pathological symptomatology was noted. For example, the first signs of recovering function of pair VII of CN were seen on day 7 ± 3.2, pair II — on day 8 ± 4.2. It was noted that impairment symptoms (algia syndrome and sensory disorders) of pairs V of CN preserved for a longer time (9.0 ± 4.3 days), as well as perimotor disorders — up to 10 ± 2.3 days. Reducing dizziness pronouncement (systemic and non-systemic) was observed in 19 (52.8 ± 8.4)% subjects on day 7 ± 4.6 of treatment, more accurate execution of coordination tests — in 16 (57.1 ± 9.5)% subjects on day 8 ± 3.5, ataxic syndrome recession — in 8 subjects on day 9 ± 4.0 of treatment. In psychical sphere we noted reducing pronouncement of emotional instability, neurosis-like syndrome, and sleep recovery in 28 (77.8 ± 7.0)% subjects on day 7.0 ± 5.0 of treatment.

During comparative analysis of the group of subjects, whose treatment was based on PT administration (I) and group, in which ANAD was administered (II), it was noted that the recessive flow of pathological physical and neurological manifestations in these groups had both common features and differences (Table 3.1).

Table 3.1

Duration of clinical symptomatology in subjects

Symptoms / syndromes	Duration (days)		$P^*_{I, V}$
	Group I, n = 36	Group II, n = 77	
Asthenic	8±2.1	9±1.9	**0.03**
Non-focal	8±1.9	8±2.2	0.1
Motor disorders	9±3.3	9±4.3	0.65
Sensory disorders	8±3.4	8±5.0	0.6
Cerebellar disorders	9±4.0	9±4.0	0.09
Cerebral nerves dysfunctions	9±4.3	9±4.3	0.48
Psychopathological syndrome	7±5.0	8±4.4	**0.04**
Pelvic organs dysfunctions	8±3.2	8±4.4	0.07
Vegetative dysfunction	9±4.7	10±3.5	**0.01**
Liquor-dynamic disturbances	9±3.5	9±4.3	0.06
Cognitive disorders	9±4.2	9±4.3	0.06
Cardialgic	8±4.8	8±4.7	0.078
Hemodynamic abnormalities	7±4.1	9±3.1	**0.001**
Dyspeptic	6±2.0	9±2.2	**0.001**
Hepatomegalia	10±6.4	11±6.9	**0.06**
Lymphadenopathy	9±1.7	9±3.8	0.93
Fever	10±1.7	10±2.3	0.78

Note: “P” was calculated according to Mann-Whitney method.

As it can be seen from Table 3.1, in two groups the similar flow ($P>0.05$) of recession of motor (day 9), sensory disorders (day 8), symptoms of CN dysfunction (day 9), cognitive disorders (day 9), cardialgic syndrome (day 8), non-focal syndrome (day 8), liquor-dynamic disturbances (day 9) was noted. The terms of lymph nodes sizes and body temperature normalization coincided too ($P>0.05$). The similar flows of symptomatology in groups can be explained by common actions of the drug’s influence on the infection process, the main of which is antiviral.

The control group subjects, as compared with study group, were reported with longer ($P<0.05$) persistence of asthenic syndrome (up to 9 ± 1.9 days), disorders in psychical sphere (up to 8 ± 4.4 days), vegetative dysfunction (up to 10 ± 3.5 days), accompanied with hemodynamic abnormalities. Pathological symptoms on the side of digestion organs were also preserved for a longer time ($P<0.05$). The steady improvements in neurological and physical statuses against the background of treatment were seen on day 7-10 (on day 8 ± 2.64 at the average) in group I, and on day 11 ± 6.2 of treatment ($P<0.05$) in group II.

As per Table 3.2, where the analysis of residual phenomena in two groups is represented, in early recovery period the modified cephalgic syndrome was observed in most subjects both in group I (83.3%) and group II (94.8%) ($P<0.05$). Cephalgic syndrome persisted the most often in group I in subjects diagnosed with ME (63.9 ± 8.1)%. No statistically significant ($P>0.05$) differences were noted in groups according to rate of recording residual sensory, motor disorders, fever and

lymphadenopathy. However, in group II, as compared with group I, psychopathological symptomatology (39%) and cerebellar disorders (39%) preserved by 1,5 times more frequently ($P<0.05$). In group I most subjects (61.1%) were observed with preserving some signs of vegetative dysfunction ($P<0.05$) at the end of treatment, despite a fast recession of most symptoms at its beginning.

The therapeutical effect was assessed as good in 16 (44.4 ± 8.4)% subjects and as satisfactory — in 20 (55.6 ± 8.4)%. Good and satisfactory effects were observed in subjects diagnosed with ME and DEM with the same rate. EMPR subjects were most frequently reported with satisfactory outcomes of treatment (in 6 of 8 subjects).

Table 3.2

Rate of registration of residual phenomena in the subjects with herpesviral impairment of nervous system depending on therapy regimen

Pathological symptoms/syndromes	Group I, n=36				Group II, n=77				P_1	P_2
	Before treatment		After treatment		Before treatment		After treatment			
	Abs.	%	Abs.	%	Abs.	%	Abs.	%		
Cephalgia	36	100	30	83.3	73	94.8	63	81.8	0.65	0.32
Psychopathological	22	61.1	8	22.2	64	83.1	30	39	0.12	**0.05**
Vegetative dysfunction	24	66.7	22	61.1	68	88.3	45	58.4	0.06	0.78
Sensory disorders	25	69.4	17	47.2	56	72.7	17	22.1	0.87	0.92
Vision disorders	24	66.7	7	22.2	51	66.2	15	19.5	0.97	0.23
Cerebellar disorders	8	22.2	5	13.9	56	72.7	30	39	0.09	**0.02**
Motor disorders	22	61.1	17	47.2	65	84.4	42	54.4	0.59	0.06
Lymphadenopathy	36	100	3	8.3	67	87.0	13	16.9	0.26	0.46
Fever	30	83.3	3	8.3	52	67.5	8	10.4	0.36	0.24

Note: The statistical significance was determined according to Fisher's exact test; P1 — before treatment, P2 — after treatment.

No reliable correlation was established between the types of therapeutic effect and such indices as: subjects' age (|r|=0.15; p=0.33), clinical form (|r|=0.19; p=0.26), etiological factor (|r|=0.05; p=0.73), severity (|r|=0.13; p=0.42), course (|r|=0.08. p=0.61) and duration (|r|=0.01; p=0.9) of disease. However, we noted tendency towards the decrease of therapeutic effect with subjects' age and increasing duration of disease. For example, good therapeutic effect was seen in subjects of 32.3 ± 12.1 years age, with the average disease duration up to 3.2 ± 0.9 years, satisfactory — in subjects of 36.3 ± 13.0 years age, with the disease duration up to 4.4 ± 0.9 years.

Table 3.3 included the main laboratory parameters for two groups against treatment.

As provided in Table 3.3, no deviations from the age-sex norm were detected (P>0.05) in general clinical, hemmostasiologic blood surveys carried out in two study groups; however, the statistically significant differences (P<0.05) were established between the groups in variations of laboratory parameters during the treatment. The statistically significant (P<0.05) increase of lymphocytes, monocytes, thrombocytes level and erythrocytes sedimentation rate was noted in the general clinical blood parameters in group I by the end of treatment course.

The short-time lyphomonocytosis in study group can be considered as normalization of immune system response to antigenic stimulation in early recovery period. As for biochemical parameters of the main group, the levels of bilirubin and creatinine remained steady (P<0.05) in the treatment process. In hemmostasiological parameters of blood for group I, as comparing with group II, by the end of treatment we noted statistically significant (P<0.05) extension of plasma recalcification time, normalization of fibrinolytic activity of plasma, preservation of steady fibrinogen level, against the background of decreasing content of fibrin degradation product in blood, which could be deemed as stabilization of fibrinolysis system activity and reducing intensity of fibrin formation. Blood and/or liquor were studied by ELISA method in all patients at the end of treatment.

Table 3.3. Dynamics of main laboratory parameters of subjects with **herpesviral infection depending on therapy regimen**

Parameters	Group I, n=36									Group II, n=77									P		
	Before treatment			Day 14 of treatment			After treatment			Before treatment			Day 14 of treatment			After treatment			P_1	P_2	P_3
	Me	LQ	UQ	Me	LQ	UQ	Me	LQ	UQ	Me	LQ	UQ	Me	LQ	UQ	Me	LQ	UQ			
Bilirubin	**12.2**	10.5	15.3	**15.1**	12.3	17.2	**15.1**	12.0	18.4	**11.7**	8.2	17.5	**12.6**	10.5	15.9	**10.5**	8.0	12.4	**0.37**	**0.19**	**0.01**
ALT	**0.3**	0.1	0.5	**0.4**	0.2	0.5	**0.4**	0.2	0.6	**0.3**	0.1	0.5	**0.4**	0.2	0.8	**0.4**	0.2	0.9	**0.35**	**0.37**	**0.27**
AST	**0.2**	0.1	0.4	**0.2**	0.2	0.3	**0.2**	0.1	0.4	**0.2**	0.1	0.3	**0.3**	0.3	0.6	**0.2**	0.1	0.4	**0.97**	**0.01**	**0.79**
Urea	**5.3**	3.9	5.6	**5.1**	4.4	5.9	**5.4**	4.4	5.8	**5.2**	4.8	5.4	**5.4**	4.9	6.3	**5.4**	4.8	5.6	**0.96**	**0.03**	**0.88**
Creatinine	**70.7**	62.5	79.1	**71.6**	62.1	84.6	**73.3**	67.8	80.4	**67.8**	53.9	78.9	**70.8**	62.3	80.9	**68.7**	58.7	75.6	**0.06**	**0.29**	**0.01**
Red blood cells	**3.5**	3.2	4.3	**3.7**	3.4	4.5	**3.5**	3.1	4.4	**3.4**	3.2	3.5	**3.0**	2.9	4.2	**3.5**	3.1	4.0	**0.01**	**0.01**	**0.8**
Hemoglobin	**130**	120	135	**132**	124	140	**134**	122	139	**134**	125	140	**125**	125	135	**120**	110	134	**0.17**	**0.06**	**0.01**
White blood cells	**7.4**	7.1	8.0	**7.2**	5.6	8.7	**7.5**	6.5	7.9	**7.2**	5.4	8.9	**7.8**	5.6	8.9	**7.2**	5.5	8.9	**0.03**	**0.22**	**0.97**
Neutrophils, stab	**3**	2	4	**2**	2	3	**3**	2	4	**3**	2	4	**3**	2	4	**3**	2	4	**0.95**	**0.57**	**0.72**
Neutrophils, segmented	**56**	51	65	**56**	50	64	**54**	48	59	**56**	51	64	**56**	50	64	**54**	48	61	**0.87**	**0.77**	**0.92**
Lymphocytes	**32**	22	39	**35**	28	38	**34**	29	39	**33**	24	38	**31**	24	35	**28**	23	34	**0.74**	**0.08**	**0.01**
Monocytes	**7**	4	9	**7**	5	10	**7**	5	10	**5**	4	8	**5**	3	7	**5**	4	7	**0.03**	**0.01**	**0.01**
ESR	**13**	10	16	**14**	10	18	**12**	10	18	**9**	6	14	**9**	6	16	**10**	7	15	**0.01**	**0.04**	**0.01**
Thrombocytes	**245**	215	305	**232**	210	275	**230**	210	280	**220**	200	265	**230**	200	290	**220**	200	260	**0.02**	**0.54**	**0.01**
PTI	**100**	80	105	**100**	88	105	**100**	90	110	**100**	88	105	**90**	80	100	**100**	88	105	**0.65**	**0.09**	**0.3**
Fibrinogen	**3.1**	2.5	3.4	**2.9**	2.3	3.7	**3.0**	2.9	3.6	**3.0**	2.5	3.3	**2.3**	2.1	3.0	**2.7**	2.6	3.2	**0.39**	**0.01**	**0.01**
Retraction time	**46.5**	42.8	54.8	**50.4**	46.1	56.3	**50.3**	45.1	60.2	**54.9**	45.3	57.5	**46.8**	46.6	56.7	**53.2**	48.7	61.3	**0.01**	**0.69**	**0.03**
Recalcification time	**115**	97	125	**120**	105	135	**112**	100	125	**115**	90	125	**100**	90	115	**100**	90	105	**0.48**	**0.01**	**0.6**
Fibrinolytic activity	**12.7**	10.2	15.6	**12.4**	10.2	15.3	**10.3**	8.3	15.3	**10.2**	8.4	15.6	**13.4**	9.0	16.0	**14.0**	10.0	19.0	**0.06**	**0.28**	**0.47**
Fibrinogen B	**+++**	+	++	**++**	-	+	**++**	+	++	**+++**	++	++	**+++**	++	++	**++**	+	++	**0.56**	**0.01**	**0.54**
Hematocrit	**0.46**	0.38	0.48	**0.4**	0.36	0.46	**0.42**	0.38	0.46	**0.44**	0.38	0.46	**0.4**	0.38	0.44	**0.41**	0.38	0.46	**0.05**	**0.34**	**0.06**
Blood clotting time	**4.0**	3.5	4.6	**4.2**	3.8	5.2	**4.4**	3.2	4.8	**3.9**	3.5	4.8	**3.8**	3.3	5.5	**4.6**	3.8	5.3	**0.05**	**0.01**	**0.01**

Note: the description was made for quantitative characteristics, which distribution differs from normal; the probability of parameters differences in the group was calculated by Friedman method; among groups — by Mann-Whitney method: P_1 — before treatment, P_2 — on day 14 of treatment, P_3 — after treatment (among groups).

Under the therapy, seroconversion of IgM class antibodies to HV was reported for all study group subjects. During repeated control (after the main therapy course had been completed, in 2-3 weeks, at the average), titres of IgM class antibodies to HV were decreasing by 20-30% versus the initial level ($P<0.05$). The decrease of level of IgM class antibodies to normal occurred averagely in 2 ± 0.8 months in group I, and within 1.5 ± 0.7 months ($P>0.05$) in group II, which spoke for the natural process of seroconversion after the period of HV replication. It was noted that lower dynamics of seroconversion was observed in subjects with EBV etiology and mixed HVI ($P<0.05$).

3.2. Adverse effects of therapy with Proteflazid

The comparative assessment of existence of any toxicity in subjects was accomplished, as well as all AE, which could be associated with drugs administration, were recorded in groups throughout the study. For example, against PT administration in group I subjects, the appearance of dyspeptic $(11.1 \pm 5.1)\%$ and gastralgic syndromes $(5.6 \pm 3.9)\%$ was observed, and in single cases, intensified general weakness $(5.6 \pm 3.9)\%$ and emergence of dryness and itching of skin covers $(2.8 \pm 2.8)\%$, being deemed as AE. The pronouncement of these AE was decreasing after adjustment of method or drug under dosing. For group II AE were registered in $61.04 \pm 5.59\%$ of subjects ($P<0.05$). For example, dyspeptic syndrome under ANAD administration was noted in 15 $(19.5 \pm 4.5)\%$ subjects, gastralgic — in 9 $(11.7 \pm 3.7)\%$, dryness and itching skin covers — in 10 $(13.0 \pm 3.9)\%$ subjects. In addition, in group II subjects the adverse effects were recorded non-typical for group I. They were hepatomegalia $(16.9 \pm 4.3)\%$, hemodynamic disorders $(19.5 \pm 4.5)\%$, transitory cytolytic and nephrotic syndromes $(16.9 \pm 4.3)\%$.

Among subjects, who were taking PT in the form of monotherapy, 6 were reported with herpetic eruptions on skin and nose and lips mucosa emerged on day 4-6 of the drug administration. The damage area was restricted, no recurrent eruptions were detected, and epithelialization took place within 5 ± 2.5 days. There were no serious AE recorded, which could threaten subjects' lives, lead to death, increase hospitalization time, result in disability and incapacitation, or were significant from medical point of view. Therefore, it can be concluded that use of PT in monotherapy form during the acute period, as opposed to ANAD therapy, is accompanied with minimal transitory AE (dyspeptic syndrome) at the most in 11.1% subjects.

The submitted data evidence for therapeutic efficacy of PT in treating subjects with HVI (therapeutic effect was good in $(44.4 \pm 8.4)\%$ of subjects, and

satisfactory in (55.6 ± 8.4)%). Better results were obtained, when treating subjects with ME. Along with antiviral action, PT possesses organs-protective properties, which improve the effects of pathogenetic drugs. Against the background of PT therapy, the terms of occurrence of improvements in physical and neurological statuses (on day 8 ± 2.6 of treatment) and in antibodies seroconversion (on months 2 ± 0.8) coincided in the study group according to the most parameters (P>0.05) versus control group, which spoke for, firstly, therapeutic efficacy of these treatment regimens; secondly — similar actions of drugs.

3.3. Interferon inducing and immunomodulatory activity of Proteflazid in subjects with herpes virus infection

3.3.1. Immunomodulatory activity of Proteflazid

For examination of immunomodulatory activity of PT, the subjects were divided into two groups — basic and control group. The basic group included 35 subjects, control group included 33 subjects — group II subjects. In Table 3.5 the dynamics of immunological parameters in subjects with HVI is represented depending on therapy regimen.

As we can see from Table 3.5, at the initial observation qualitative and functional impairments of the cellular component of immune system and neuroautoimmune reactions were noted in subjects of both groups. No statistically significant differences in immunological parameters of subjects from both groups were detected before the beginning of treatment (P1>0.05).

Table 3.5. **Immunological parameters dynamics, subject to the therapy pattern**

Immunological parameters	Norm	Basic group, n=35							Control group, n=33							P_1	P_2
		Before treatment			After treatment			P_o	Before treatment			After treatment			P_c		
		Me	LQ	UQ	Me	LQ	UQ		Me	LQ	UQ	Me	LQ	UQ			
Lymphocytes, %	30-36	39.3	35.0	45.0	39.2	34.0	45.0	0.8	40.1	36.0	45.0	39.8	36.0	43.0	0.88	0.8	0.2
CD-3, %	56-65	52.7	49.0	64.0	56.5	52.0	65.5	0.4	54.9	45.0	59.0	53.8	44.3	63.3	0.64	0.5	0.1
CD-4, %	25-35	30.4	24.7	34.5	33.2	27.9	35.1	0.1	32.3	25.7	39.1	34.6	29.7	37.8	0.1	0.5	0.2
CD-8, %	22-26	24.4	21.2	27.6	27.4	21.9	28.9	0.18	27.3	23.6	29.7	27.0	24.1	28.5	0.81	0.06	0.3
CD-20, %	8-10	12.2	8.3	15.9	10.2	6.9	12.9	**0.01**	9.7	7.6	12.0	10.5	8.8	12.8	0.36	0.07	0.5
CD-16, %	17-20	15.2	10.3	18.9	17.9	14.3	19.3	0.12	18.2	12.4	21.4	14.7	11.9	16.8	**0.04**	0.05	**0.01**
Spontaneous proliferation of lymphocytes in BTR, %	0-2	4.8	2.0	6.0	3.3	2.0	4.0	0.12	5.1	2.0	8.0	4.4	2.0	6.0	0.36	0.8	0.06
T-mitogen proliferation of lymphocytes, %	55-65	60.2	53.0	68.0	55.1	53.0	62.0	0.13	54.4	48.0	63.0	54.5	51.0	62.0	0.96	0.1	0.5
Prostaglandin-dependent proliferation of lymphocytes, %	65-75	69.9	59.0	82.0	62.6	56.0	73.3	0.06	60.8	49.0	76.0	58.1	554.0	64.0	0.61	0.06	0.2
B-mitogen proliferation of lymphocytes, %	30-45	47.0	39.0	56.0	45.1	38.0	54.0	0.13	45.8	32.0	55.0	39.0	31.0	47.0	**0.04**	0.9	**0.02**
Spontaneous MCC, %	26-34	25.0	21.0	32.0	31.5	28.0	34.0	**0.03**	28.0	25.0	34.0	28.5	25.0	35.0	0.25	0.3	0.9
Antibody-dependent MCC, %	42-50	35.6	28.0	45.0	41.3	37.0	45.0	0.07	41.6	34.0	51.0	43.8	36.5	49.0	0.83	0.1	0.2
CIC, RVU	70-80	124.3	95.0	150.0	102.6	82.5	120.2	**0.02**	121.5	95.0	130.0	99.4	80.0	120.0	**0.01**	0.7	0.6
Spontaneous neutrophil phagocytic rate, RVU	255.0	263.8	228.0	296.5	259.5	245.0	276.0	0.33	256.5	215.8	290.0	255.7	246.0	274.0	0.81	0.2	0.8
Induced neutrophil phagocytic rate, %	60-70	55.5	50.6	60.7	60.1	56.0	65.4	**0.003**	57.5	53.1	65.4	58.0	54.5	62.5	0.76	0.09	0.4
Neutrophil adhesive activity, %	35-55	39.5	32.0	48.0	43.0	34.0	53.0	0.22	41.1	34.0	48.0	39.6	33.0	46.0	0.48	0.8	0.2
Autoantigen (TPM) induced proliferation in BTR, %	0-3	8.4	5.0	12.0	6.7	5.0	10.0	0.1	6.6	6.0	10.0	7.6	6.0	9.0	0.26	0.6	0.2
Sensitization of neutrophils to albumin, %	5-20	20.4	12.0	31.0	16.3	10.0	16.0	0.07	17.7	8.0	25.0	13.3	8.0	15.0	0.17	0.5	0.7
Sensitization of neutrophils to TPM, %	5-7	22.2	11.0	25.0	14.1	8.5	15.5	**0.001**	25.9	13.0	39.0	16.0	8.0	14.5	**0.009**	0.2	0.7
Sensitization of neutrophils to NSE, %	3-6	24.4	12.0	31.0	15.0	9.5	14.5	**0.003**	28.1	12.0	38.0	15.6	8.0	14.5	**0.006**	0.3	0.8
ELISA level of autoantibodies (MBP), RVU	25-27	35.7	35.7	36.7	23.7	21.7	27.8	**0.003**	29.2	22.7	31.7	25.5	21.9	28.9	0.17	0.9	0.6

Note: Me — median, LQ — lower quartile, UQ — upper quartile; P_o — in basic group calculated according to Wilcoxon test; P_c — in control group calculated according to Wilcoxon test; P_1 — before treatment, calculated according to Mann-Whitney test; P_2 — after treatment, calculated according to Mann-Whitney test.

At the repeat examination we noted improvements in all subjects' immune statuses in the form of decreasing level of CIC by 17% and parameters of immunization to neurospecific antigens (TPM, NSE) twofold at the average versus the initial value ($P<0.01$). However, despite the improvements observed, at the end of treatment, level of CIC and immunization of lymphocytes to neurospecific proteins remained exceeding the maximal permitted level by 25% and 50%, accordingly ($P<0.05$).

Against the background of PT therapy, basic group subjects were reported having statistically significant decrease of overall B-lymphocytes by 17% ($P_o<0.01$) and level of antibodies to tissue-specific antigens (TPM) by 40% versus the initial value ($P_o<0.01$). We also identified that the parameters of spontaneous MCC and induced neutrophil phagocytic rate increased in a statistically significant manner ($P_o<0.05$) by 20% ($P_o<0.05$) and 10% ($P_o<0.01$), respectively.

During repeated immunological investigations in control group, the statistically significant ($P_c<0.05$) decreasing quantity of natural killers by 22% was observed, as well as increasing functional activity of B-lymphocytes in blast-transformation reaction in response to lipopolyssacharide stimulation by 15%.

At the repeated observation, we detected statistically significant variations ($P2<0.05$) between immunological parameters in the subjects of both groups. For example, basic group subjects, as opposed to group II, at the end of treatment were reported with more pronounced increase of overall number of T-lymphocytes (CD-3) by 7%, natural killers (CD-16) by 17% and increasing functional activity of mononuclears (by 20%) and neutrophils (10%), which evidenced a sustainable tendency to normalization of the cellular component of immune system against PT therapy.

Consequently, PT possesses moderate immunomodulatory properties, which manifest themselves in normalizing cellular component of immune system (increasing number of natural killers by 17%, functional activity of mononuclears (by 20%) and neutrophils (10%)) and reducing pronouncement of neuroimmune reaction by more 1.5 times.

3.3.2. Interferon inducing properties of Proteflazid

The dynamics of IFN activity in blood serum of HIV-infected subjects against the background of PT administration is represented in Table 3.6.

Table 3.6

Dynamics of α- and γ-interferons activity in blood serum of subjects with herpesviral infection against Proteflazid

Observation time (day)	Interferon type			
	pH+		pH+	
	(un/ml)	Log ± m	(un/ml)	Log ± m
Before the drug administration	14	3.8 ± 1.0	97	6.6 ± 1.1
1st	26	4.7 ± 0.9	69	6.1 ± 1.6
2nd	—	—	28	4.8 ± 0.2
3rd	—	—	112	6.9 ± 1.8
7th	—	—	91	6.5 ± 0.7
10th	23	4.5 ± 1.7	52	5.7 ± 0.98
20th	52	5.6 ± 1.0	37	5.3 ± 0.9
30th	45	5.5 ± 2.0	—	—
6th month	48	5.6 ± 1.8	34	5.1 ± 0.8

As it can be seen in table 3.6, at the initial observation the subjects were reported with α- and γ-interferons, and α-IFN activity did not exceed 14 un/ml, at the same time.

On the first day of PT administration, α-IFN activity was increasing up to 26 un/ml. Further, from day 2 to 9 we noted IFN activity tending to γ-IFN ($P<0.05$), which maximal titer (112 un/ml) was identified on day 3 of treatment. Starting from day 10, α-IFN induction was observed to prevail (in 23-45 un/ml titer). The investigation of IFN activity on subjects after 6 months of continuous administration of the drug revealed a moderately increased α-IFN level (48 un/ml).

When analyzing interrelations between the dynamics α- and γ-IFN and clinico-therapeutic efficacy, it was detected that the sustainable improvements in neurological and physical statuses of the basic group subjects started from day 9-10 of treatment, which coincided with IFN activity shift (Fig. 3.1). Our opinion is that 7-day period of increase of γ-IFN activity encouraged correction of immunological disorders, inhibition of viruses' replication and achievement of homeostasis stabilization. The following anti-relapsing effect obtained due to the long-term use of PT is ensured by steadily increased α-IFN activity. Therefore, the ability of PT to induce γ-IFN and change of induction of various IFN types represents one of the main actions of its anti-herpesviral and immunocorrective effect at HVI within acute

phase, and ability of the drug to support a steadily increased α-IFN level — its main anti-relapsing mechanism of action.

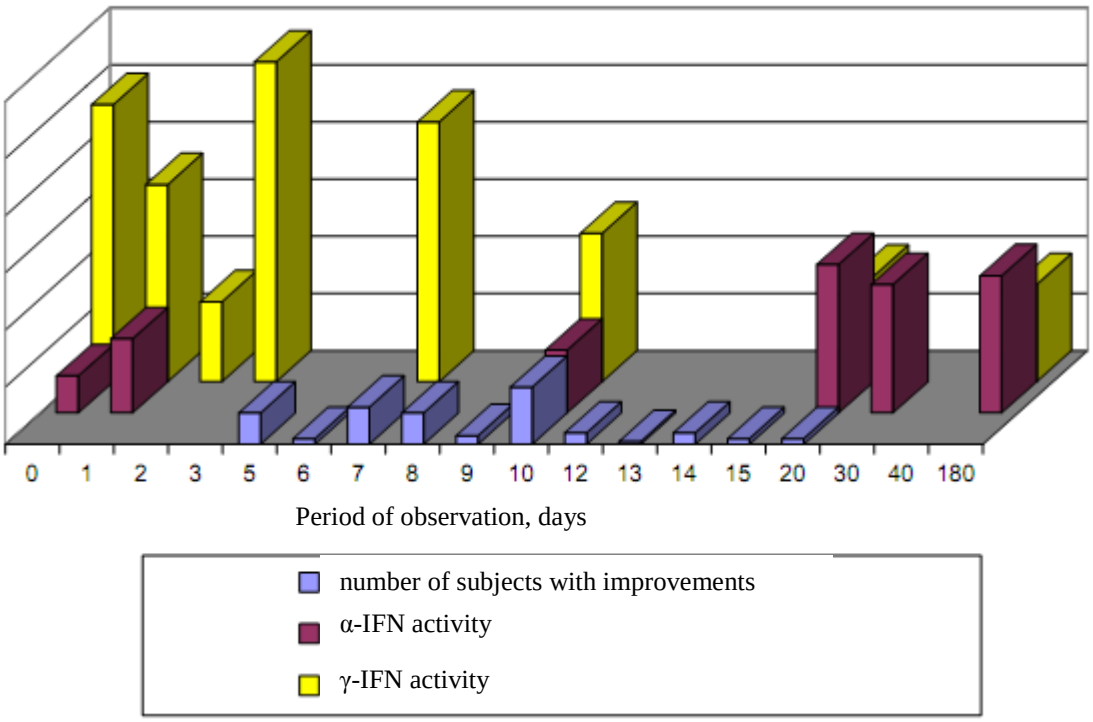

Fig. 3.1. Interrelation of interferon induction course with the periods of clinical improvement onset in subjects.

It is also important that during daily administration of drug no inhibition of α- and γ-IFN activity was detected, which speaks for the absence of immunotropic cells' refractivity to interferon induction with PT.

When examining interrelation between immunological parameters and IFN activity dynamics, it was noted that the basic group subjects, as compared with control, against PT therapy experienced the moderate increase of natural killer's number and mononuclears and neutrophils functional activity, which may be deemed as the consequence of γ-IFN action on immune cells. It is important since HVI subjects are reported for virus-induced immunological impairments manifesting in reduction of quantitative (CD-16) and functional parameters of cellular component of immune system and neuroimmune reactions development.

That way, Proteflazid possesses therapeutic efficacy in monotherapy against moderately severe, DNA-negative HIV forms (good therapeutic effect was recorded in 44.8 ± 8.4% of subjects, satisfactory — in 55.6% of subjects):

- recession of the main neurological and physical symptomatology is observed on day 8 ± 2.6 of treatment ($P<0.05$);

- seroconversion of specific antibodies in all subjects competes within 2 ± 0.8 months;
- correction of immunological disorders in the form of increasing overall number of natural killers (CD-16) by 17% ($P<0.01$), increasing functional activity of mononuclears by 20%, neutrophils — by 10% ($P>0.05$);
- good tolerability and safety of therapy (AE were observed only in 11.1% of cases). (See Fig. 3.2).

PT has moderate interferon inducing properties. The dynamics of induction of interferon formation when treating HVI subjects is characterized with prevailing activity of γ-IFN from day 2 to 9 accompanied by further increase of α-IFN starting from day 10 and during all the following period of drug administration. The interferon conversion time coincides with the time of clinical improvements onset.

The detected immunomodulatory and interferon inducing activity of PT justifies the drug prescription to HVI-infected subjects: 1) in the form of monotherapy or complex therapy of severe or moderate course of HV process for potentiation of anti-viral effect; 2) in the form of long-term anti-relapsing treatment in the period of recovery.

CHAPTER 4
LONG-TERM RESULTS OF TREATMENT OF HERPES VIRUS INFECTION

4.1. Anti-relapse efficacy of Proteflazid

The main criterion of therapeutic efficacy of any antiviral therapy is its anti-relapse activity. In order to examine anti-relapse activity of the proposed treatment regimens, we were conducting a dispensary follow-up of all (236) subjects, who participated in the study, during 1-2 years. The survivors were under regular (each 2-3 months) physico-neurological and virusological observations within this period, which enabled assessing the nature of early and late recovery periods.

Following the results of the first therapy course, all basic group subjects were separated into 3 groups (fig. 4.1):

1) subjects, who recovered clinically, having no relapses or exacerbations of residual neurological or physical pathology within the entire follow-up period (up to 2 years) — 121 (51.3 ± 3.3)% subjects;

2) with virus “+” relapses — detection of signs of recovering replicative activity of viruses in blood and/or CSF by PCR, ELISA methods against the emergence of

new symptom or group of symptoms on the side of NS, internal body parts or pronounced acerbation of earlier existing symptoms, after when the subject's condition was steady during 2-3 months — in 25 (10.6 ± 2.0)% subjects;

The "virus "+" notion included detection of recovering replication of viruses, which have been etiological disease factors previously in the form of mono- or mixed HVI.

3) with virus "-" relapses — the emergence of new symptom or group of symptoms on the side of NS, internal body parts or pronounced acerbation of symptoms, not associated with activation of earlier existing viruses — in 90 (38.1 ± 3.2)% subjects.

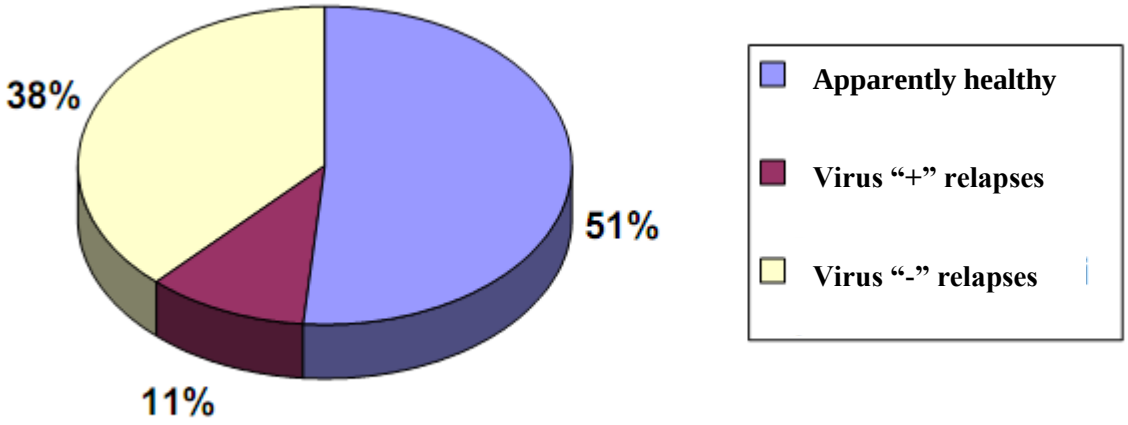

Fig. 4.1. Distribution of subjects (%) according to the nature of recovery period

After the basic treatment course, 159 subjects continued PT administration for anti-relapse purpose according to the abovementioned patterns (see Chapter 2.2). The control group included subjects from group II, who did not take PT. All of them were followed-up during 1-2 years after the discharge.

Table 4.1 features a rate of emergence of virus "+" and virus "-" relapses in recovery period depending on the nature of anti-relapse therapy.

Table 4.1

Rate of relapses depending on the therapy in recovery period

Attributes	Basic group, n=159		Control group, n=77		P
	Abs.	%	Abs.	%	
Virus "+" relapse	**13**	**8.2 ± 2.2**	**12**	**15.6 ± 4.2**	**0.04**
Virus "-" relapse	**55**	**34.6 ± 3.8**	**35**	**45.5 ± 5.7**	**0.06**

Note: "P" was calculated by the Fisher's angular transformation method.

As we can see in the table, in the group of subjects, who continued PT administration, the rate of virus "+" relapses was in by 1.9 times more seldom ($P<0.05$), and rate of virus "-" relapses — in 1.3 times less ($P>0.05$) than in control. Therefore, the drug promotes statistically significant reduction of virus "+" relapses rate of disease, but never affects virus "+" rate.

Virus "+" relapses of disease were more often recorded for subjects with EBV (21.1 ± 9.6)% and HSV+CMV (26.3 ± 10.4)% etiology in basic group, and among subjects with HSV (33.3 ± 14.2)% and HSV+CMV (33.3 ± 14.2)% etiology in control group with the same rate. The virus "+" relapses were encountered among the subjects with monoviral and mixed HVI with the same rate both in basic and control groups. In cases with earlier mixed HVI in 12 (85.7 ± 9.7)% subjects we noted recovery of replication of one of HV types, which formerly were incorporated in mixture, CMV is the most often (55.6 ± 17.6)%.

The virus "-" relapses were more often reported for subjects with HSV (21.8 ± 5.6)%, HSV+CMV (21.8 ± 5.6)% and HSV+CMV+EBV (18.2 ± 5.3)% etiology in basic group. Beside the mentioned HV types and mixtures thereof, in control group we detected EBV (14.3 ± 6.0)% and combination of viruses HSV+EBV (14.3 ± 6.0) often enough. No correlations between etiological factor and nature of recovery period were observed ($r=0.02$; $p=0.52$), however, the tendency was noted for complication of the course of recovery period in subjects, in which HSV and EBV were etiological factors of monoviral infection, and combination of viruses HSV + CMV — of mixed HVI.

Table 4.2 features the etiological structure of HVI in subjects reported with relapses and exacerbations of residual phenomena.

No correlational relationship was established between the clinical form, disease severity and rate of virus "+" and virus "-" relapses ($r=0.01$; $p=0.7$), but it was noted that virus "+" relapses were reported in most cases for the basic group in ME (63.2 ± 11.4)% and EMPR (31.6 ± 11.0)% subjects mainly in a moderate manner (73.7 ± 10.4)%, and similar tendency was seen in the control group too (75.0 ± 13.1%, 25.0 ± 13.1% and 75.0 ± 13.1%, respectively).

Table 4.2

Relationship between etiological factor and nature of recovery period depending on treatment regimen

Virus/mixture type	Study group	
	Basic group, n=159	Control group, n=77

	Abs.	%	Abs.	%
Virus “+” relapse	13	8.2 ± 2.2	12	15.6 ± 4.2
HSV	2	10.5 ± 7.2	4	33.3 ± 14.2
CMV	1	5.3 ± 5.3	2	16.7 ± 11.2
EBV	4	21.1 ± 9,6	1	8.3 ± 8.3
HSV+CMV	5	26.3 ± 10.4	4	33.3 ± 14.2
HSV+EBV	1	5.3 ± 5.3	—	—
HSV+CMV+EBV	—	—	1	8.3 ± 8.3
Other types of mixtures	2	10.5 ± 7.2	—	—
Virus “-” relapse	55	34.6 ± 3.8	35	45.5 ± 5.7
HSV	12	21.8 ± 5.6	11	31.4 ± 7.9
CMV	1	1.8 ± 1.8	3	8.6 ± 4.8
EBV	6	10.9 ± 4.2	5	14.3 ± 6.0
HSV+CMV	12	21.8 ± 5.6	6	14.3 ± 6.0
HSV+EBV	5	9.1 ± 3.9	5	14.3 ± 6.0
HSV+CMV+EBV	10	18.2 ± 5.3	3	8.6 ± 4.8
Other types of mixtures	9	16.4 ± 5.0	2	5.7 ± 3.9

Etiological factors were somewhat differing in subjects with virus “-” relapses. For example, in basic group virus “-” relapses were recorded more often in ME (59.7 ± 6.6)% subjects and almost with the same rate — in DEM (19,3 ± 5.3)% and EMPR (21.1 ± 5.5)% subjects. In control group, in subjects with EMPR, versus basic, they were almost absent (6.1 ± 4.2)%, but the rate of DEM exacerbations was higher (24.2 ± 7.6)%. It was typical that virus “-”relapses in the form of intensification of pathological neurological symptomatology were more often registered in females (78.2 ± 5.6)% both in basic and control groups. Under such circumstances in basic group, the challenging factors were stress in 29 (52,7 ± 6.8)% and addition of acute respiratory viral infection in 13 (23.6 ± 5.8)% subjects. 13 subjects could not provide any reason for deterioration of condition. At relapses the state of 64 (86.5 ± 4.0)% basic group subjects was assessed as moderate, and in 10 (13.5 ± 4.0)% — as mild. No severe conditions were registered in basic group subjects. In most cases, one or several pathological neurological syndromes were observed to prevail in neurological status of this group subjects during relapses. Non-focal syndrome (87.8 ± 3.8)%, motor (47.3 ± 5.8), sensory (43.2 ± 5.8) and cerebellar disorders (36.5 ± 5.6) were intensifying in most cases. Intensification of pathological signs on the CN part, psychopathological syndrome, comparing to the initial observation, was registered less frequently (24.3 ± 5.0% and 43.2 ± 5.8%, respectively). Positive clinical effect in 55 basic group subjects with the false relapses was gained against a pathogenetic therapy. The repeated antiviral treatment was undertaken in 13 (8.2 ± 2.2)% subjects with virus “+” relapse. The time of the condition stabilization against treatment was noted on day 7±2.5 of treatment, which was by 1-1.5 days earlier than at the initial course.

At relapses the conditions of 3 (6.4 ± 3.6)% subjects were considered as severe, in 38 (80.9 ± 5.8)% subjects — as moderate, and in 6 (12.8 ± 4.9)% subjects — as mild in the control group. As opposed to basic group, 3 subjects of this group diagnosed with DEM and EMPR during repeated admission to the hospital against the virus "+" relapse of disease were registered with deterioration of the condition as compared with previous revisions. In clinics we noted cellular neurological symptomatology to prevail cerebral. In all 12 virus "+" relapses, the subjects were provided with complex ethiopathogenetic therapy with the change of antiviral drug. In virus "-" relapses, the subjects were provided with pathogenetic treatment course including PT in the treatment regimen. The steady positive clinico-neurological effect was achieved in the control group on day 10 ± 3.5 of treatment, which was 1 day earlier ($P<0.05$) than at the initial therapy course, but 2 days later than in the basic group ($P<0.05$).

That way, for subjects with HV impairments of NS there is a high probability of development of virus "+" (10.6 ± 2.0)% and virus "-" (38.1 ± 3.2)% relapse after completion of a main therapy course. In most cases, complicated recovery period is observed in females (70.4 ± 4.3), ME (66.1 ± 4,4)%, EMPR (66.1 ± 4.4)% subjects, subjects with moderate disease course and such etiological factors as HSV (27.8 ± 4.2)%, EBV (13.0 ± 3.2), HSV+CMV (24.4 ± 4.0)%. We noted tendency for increasing rate of virus "+" relapses and reducing intercurrent period in groups, where the main therapy course was provided without ANAD, however, this observation is statistically minor ($P>0.05$). The absence of interrelation between the rate of virus "-" relapse and nature of ethiopathogenetic therapy, and approximately the same time of occurrence thereof in groups, speak for any other nature of these phenomena. The long-term use of PT after the main therapy course according to specially developed patterns promotes reduction of rate of virus "+" by 1.9 times ($P<0.05$) and virus "-" relapses by 1.3 times ($P>0.0.5$), encourages relief of severity of subjects' conditions during this period and reduction of time of improvements achievement.

CONCLUSIONS

This paper comprises generalizes theoretical and practical data on ethiopathogenetic and clinical peculiarities of herpesviral infection. It contains a new solution for challenging scientific task — improvement of efficacy of treatment and prophylaxis against recurring herpesviral infection by virtue of two-stage ethiopathogenetic therapy with the use of Proteflazid.

1. In modern etiological structure of herpesviral infection the mixtures of herpesviruses prevail (59.3 ± 3.2)%, which are in most cases detected in chronic

subjects. The majority is combinations of viruses with the different sensitivity to acyclic nucleoside antiviral drugs (HSV+CMV — 22.9% HSV+CMV+EBV — 15.3% HSV+EBV — 8.1%), which result in complications when selecting etiotropic treatment. Monoherpesviral infection is observed in 40.7 ± 3.2% subjects, mainly with the acute onset of disease (in 19.5% — HSV1/2, 13.1% — EBV and 8.1% — CMV).

2. Body impairment at herpesviral infection is of a systemic nature. Key role in the origin of neuroinfectious pathology belongs to HSV, visceral pathology and hemmostasiologic disorders — EBV and CMV. In most cases, pathological manifestations structure features asthenic (100)%, cephalgic (97.9 ± 1.0)% syndromes, insufficiency of cerebral nerves function (75.4 ± 2.8)%, psychical (72.0 ± 2.9)%, liquor-dynamic (58.5 ± 3.2)%, sensory (53.8 ± 3.3)% and vegetative (77.1 ± 2.7)% disturbances, lymphoadenopathy (94.9 ± 1.4)%, fever (81.4 ± 2.5)% and moderate hepatomegalia (59.8 ± 3.2)%.

3. Subjects with herpesviral infection experience cellular and humoral components of immune system disorders: reduction of NK-cells number, inhibition of mononuclears and neutrophils activity against the background of more than twofold, versus normal, increase of number of circulating immune complex ad antibodies to total myelin protein and parameters of lymphocytes immunization to neurospecific proteins.

4. In the scope of monotherapy of moderate and non-complicated forms of herpesviral infection Proteflazid possesses a moderate clinico-immunological efficacy typified by the recession of physic-neurological symptomatology on day 8 ± 2.6 of treatment; seroconversion of specific antiviral antibodies on month 2.0 ± 0.8 of treatment; increase of number of NK-cells by 17%, functional activity of mononuclears by 20%, neutrophils by 10% and decrease of neuroautoimmune reactions pronouncement by 1.5 times. Any adverse effects against Proteflazid administration were observed in 11% of subjects. (See fig. 3.2.)

5. The dynamics of induction of interferon formation against Proteflazid administration is characterized by prevailing γ-interferon activity, firstly, with the further increase of α-interferon. Under condition of daily intake of the drug, no inhibition of α- and γ-IFN is observed, which evidences the absence of refractivity of immunotropic cells to IFN induction.

6. In 48.7% of survivors, after the treatment we provided, some relapses were observed, which were accompanied with recovery of replicative activity of viruses only in (27.1 ± 3.9)% cases. Use of Proteflazid during recovery period make it possible to reduce rate of recurrent clinico-virusological (virus “+”) relapses in 1.9 times, clinical (virus “-”) relapses — by 1.3 times, as well as relieve the disease

severity and accelerate achievement of therapeutical effect during repeated therapy of relapse.

PRACTICAL GUIDELINES

1. Subjects with the suspected herpesviral infection should undertake investigations of several biological media at the same time (CSF, blood, saliva, urea) and complex clinico-laboratory examination for the purpose of timely detection of virus-induced physical disturbances. For subjects with nervous system impairments, study of CSF, immunological and hemmostasiologic blood parameters are mandatory.

2. Therapy for the subjects with herpesviral infection should consist of 2 stages: first (1-2 months) — basic course of ethiopathogenetic therapy, second — the long-term (6-12 months) anti-relapse therapy with Proteflazid.

3. Proteflazid in monotherapy scope (30 drops a day within 2 months) is permitted for use in subjects: 1) with mild or moderate disease course without the signs of rapid disease progression; 2) with DNA-negative forms (detection of only IgM and IgG diagnostic titres in blood) of herpesviral infection; 3) with prevailing monosyndrome; 4) with the severe subcompensated concomitant pathology; 5) with hard allergic reactions to chemical antiviral drugs in the past history.

4. Inclusion of Proteflazid in complex treatment regimens enables reducing course dosage of acyclic nucleoside drugs by 20%, at least.

5. Proteflazid is recommended for anti-relapse purpose:

a) to subjects, who meet even one of below criteria, for a year (firstly, 3 times a day: 10 drops within the first 6 months, afterwards: 8 drops within 3 months, further: 5 drops within 2 months, and 5 drops once a day during the last month):

- presence of CMV and/or EBV infection;
- presence of mixed herpesviral infection;
- disease duration for more than 3 years;
- presence of severe or chronic disease course with relapses (rate of relapses should exceed 2 per a year).

b) to subjects, who had no signs above listed — within 6 months (firstly, 3 times a day: 10 drops within the first 3 months, afterwards: 8 drops within 1 month, further: 5 drops within 1 month, and 5 drops once a day during the last month).

6. All subjects with herpesviral infection with the nervous system impairment phenomena are recommended to undertake simultaneous observation of infectiologist

and neurologist 2 times a year with periodical (each 3 months — during the first year) somatoneurologic, virusologic and immunologic examinations in order to timely detect the disease relapse and provide antiviral therapy.

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