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Determination of the Prevalence of Postcovid Syndrome and Assessment of the Effectiveness of the Drug Cortexin in the Treatment of Neurological Disorders in Patients with Postcovid Syndrome. Results of the CORTEX Multicenter Clinical and Epidemiological Observational Program

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Objectives. To study the prevalence and clinical manifestations of postcovid syndrome (PCS) in out-patients and to assess the efficacy of treatment with the drug Cortexin at doses of 10 and 20 mg i.m. for 10 days. **Materials and methods.** A total of 979 patients with PCS from regions of the Russian Federation, Azerbaijan, Kyrgyzstan, and Kazakhstan were studied; mean age was 54.6 ± 4.5 years; duration of COVID-19 was from one month upwards. Investigations involved three visits. The first was on the day of consultation (assessment of complaints, analysis of scale indicators, prescription of drug Cortexin at a dose of 10 or 20 mg i.m. for 10 days). The second visit (telephone consultation) was on day 10–14. The third visit was on day 30 of out-patient treatment. Assessment of patients' status used an asthenia assessment scale (MFI-20), a brief mental state assessment scale (MMSE), the Schulte test, and the Subjective Treatment Quality Assessment Scale. **Results.** The proportion of patients with PCS was up to 30% of all neurological admissions. The commonest manifestations were: fatigue, general weakness, decreased memory and concentration of attention, vertigo, sleep impairment, irritability, and aggression; less frequent were breathlessness, pain, increased sweating, anosmia, hyposmia, dysgeusia, paresthesia, hair loss, degradation of vision, tachycardia, allergic reactions, menstrual cycle impairments, erectile dysfunction, panic attacks, suicidal ideation, depression and refusal to eat meat. **Conclusions:** No associations were found between clinical symptomatology and the severity of COVID-19, the volume of lung tissue affected, or different periods of postcovid syndrome. Cortexin was found to be effective at doses of 10 and 20 mg for correcting the cognitive and asthenic manifestations of PCS. Cortexin was found to have anti-anxiety, antidepressant, and anxiolytic effects, which were more marked at the 20-mg dose.

Keywords: SARS-CoV-2, COVID-19, postcovid syndrome, prevalence, fatigue, cognitive impairment, olfactory impairment, Cortexin.

Postcovid syndrome (PCS) includes the sequelae of coronavirus infection COVID-19, where up to 20% of patients display a diversity of symptomatology for 12 weeks or longer [1–4]. There are currently no consistent data on

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the incidence of PCS, as the frequencies of occurrence are different in different countries [3]. There are also difficulties in providing complete descriptions of its clinical manifestations and possible therapeutic strategies [4–6]. There are various directions in the treatment of PCS, often employing antioxidants [7], though minimization of the harmful actions of reactive oxygen species may be insufficient in relation to preventing virus-mediated cell damage [8–10]. Adaptation of neurons to damage needs to be increased, and their viability in unfavorable conditions needs to be enhanced. Excessive quantities of proinflammatory cytokines, particularly interleukin (IL)-1, lead to expression of brain-derived neurotrophic factor (BDNF), so restoration of neurotrophics is linked with the extent of reductions in the severity of the cytokine storm, such that use of neurotrophic factors such as BDNF and nerve growth factor (NGF) is indicated [9, 10]. BDNF induces the expression of nuclear transcription factor NF-ϰB, which regulates the activation, differentiation, and effector function of inflammatory T cells and inflammasomes. This can occur on activation of the BDNF-dependent TrkB signal transmission pathway for neurotrophins, which are responsible for synaptic plasticity [11]. Transmission of TrkB signals, particularly in the TrkB/phosphatidylinositol-3-kinase/protein kinase B pathway, promotes the activation and nuclear translocation of Nrf2, thus providing the neuron with protection against direct and indirect viral damage [9]. Increases in the number of activated glial cells and the concentrations of various cytokines in the hippocampus, cerebral cortex, substantia nigra, and striatum (particularly tumor necrosis factor TNF-α) are associated with decreases in hippocampal volume and the onset/progression of cognitive impairments [8]. In conditions of severe viral aggression, the blood:brain barrier (BBB) remains a hindrance to delivery of therapeutic substances, so small endogenous peptides which, not themselves neurotrophins, interact with the cognate receptors, stimulate the synthesis of releasing factors in the corresponding brain areas and easily cross the BBB [10, 12].

So-called SMART peptides play a special role; these have high selectivity, efficacy, and safety [13]. The use of SMART peptides can be regarded as a key pharmacological strategy in the therapy of PCS, due to their ability to bind selectively, self-assemble, and produce adequately powerful biological responses [14]. Members of this class of drugs include Cortexin [15, 16], which is able to exert direct and indirect neurotrophic influences on cells, stimulating neurite growth or preventing the death of neurons in culture without growth factors [14, 15]. Cortexin has systemic and local anti-inflammatory effects, significantly reduces IL-1 and TNF-α levels, interacts with creatine kinase BB, influences energy metabolism to provide a neuroprotective effect in hypoxic conditions, increases intracerebral serotonin and adrenaline metabolism, stimulates the bottom-up noradrenergic system, and has membrane-stabilizing and antioxidant effects [14, 15]. Hyperexpression leads to decreased adhesion of leukocytes to the endothelium and their migration across the endothelium, decreases proinflammatory cytokine expression, and increases the density of the blood:brain barrier (BBB), which reduces its permeability [17]. Cytoskeletal proteins, interacting with Cortexin (actin, 14-3-3-α/β protein), form tight junctions in the vascular endothelium, promoting maintenance of BBB integrity, which is extremely important in conditions of viral infection [18]. The drug, acting on GABA receptors and ionotropic metabotropic glutamate receptors, prevents excitotoxicity and promotes optimization of excitation and inhibition processes, which is clinically important for patients with chronic cerebral ischemia (CCI) and cephalgic and vestibuloatactic syndromes [18]. All four identified brain proteins interacting with Cortexin (tubulin β5, creatine kinase BB, 14-3-3-α/β protein, and actin) support the maturation and insertion of young neurons into neural networks, regulate enzyme activity, protect against protein dephosphorylation, and drive sequestration and neuroprotection processes in neurodegenerative diseases [18]. The main mechanisms of these processes are based on changes in the expression of genes regulating the synthesis of neurotrophic factors BDNF and NGF [19].

The aim of the CORTEX multicenter clinical-epidemiological observational program is to study the prevalence and clinical manifestations of PCS in patients at out-patient neurological clinics and assess the efficacy of treatment with the drug Cortexin at doses of 10 and 20 mg i.m. for 10 days.

Materials and Methods. A total of 674 neurologists from all regions of the Russian Federation, Azerbaijan, Kyrgyzstan, and Kazakhstan took part in the CORTEX observational program. *Inclusion criteria:* signed informed consent to take part in the program; history of COVID-19 (confirmed by ELISA or PCR); onset of persistent complaints after COVID-19 which were not usual for the patient; presence of clinical manifestations of PCS in the form of asthenic syndrome (>12 points on one of the MFI subscales) or moderate cognitive disorder (25–28 points on the MMSE); and age 18–80 years. *Noninclusion criteria:* Acute respiratory viral infection and COVID-19 in the acute stage; severe cognitive or mental impairments; severe or unstable arterial hypertension (AHT); arterial blood pressure (BP) >200/115 mmHg; decompensated somatic diseases – ischemic heart disease (IHD), chronic pulmonary, renal, or hepatic failure, oncological diseases; other (nonvascular) central nervous system diseases; acute cerebrovascular impairments in the last month before inclusion in the study; age under 18 or over 80 years; pregnancy or breastfeeding; presence of gross motor or sensory defects or other severe diseases or conditions which in the view of the medical investigator could distort the results of the observational program or limit the patient's participation in the study; intolerance of components of the drug; therapeutic allergy or other contraindications to use of the drug Cortexin. *Exclusion criteria:* occurrence of any condition in the noninclusion list; protocol violations; individual drug intolerance; pa-

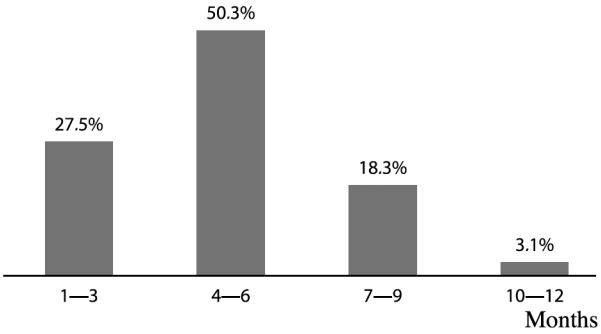

Fig. 1. Distribution of patients depending on duration of COVID-19.

tient's or patient's relative's request; any medical (including serious adverse events (AE)) or social (change in place of residence, long business trips) events forcing termination of study participation.

The study included a total of 979 patients who had had COVID-19; mean agonist was 54.6 ± 14.5 years (range 18–80 years); 328 were male and 651 were female. The duration of SARS-CoV-2 was 1–12 months Fig. 1). Diagnoses of COVID-19 were confirmed by PCR in 405 patients, PCR and chest CT in 212, and ELISA and/or computerized tomography (CT) of the lungs in the remainder (chest CT was not performed in 100 patients). In 258 patients (26.4%), lung involvement by CT was <25%, in 519 (53.1%) there was no lung involvement, in 111 patients (11.3%) lung involvement was <50%, and in 15 patients (1.5%) it was 51–100%. Most patients had mild or moderate infections. One third of patients received treatment in hospital, among whom 10 were admitted to the resuscitation and intensive therapy department. All patients received specific treatment for COVID-19; 464 (47.4%) of patients received treatment for concomitant diseases as indicated (antihypertensives, hypoglycemics, antithrombotics, statins).

All patients complained of symptoms persisting long after infection, which were not associated with other diseases and were confirmed by investigation results and consultation with specialists: therapists, cardiologists, endocrinologists, rheumatologists, ophthalmologists, trichologists. Patients with severe anxious-depressive disorder for >3 months consulted a psychotherapist/psychiatrist.

Among concomitant diseases, 525 patients (53.6%) had AHT, 133 (13.6%) had diabetes mellitus, 262 (26.8%) had atherosclerosis, 248 (25.3%) had chronic cerebral ischemia, 124 (12.7%) had IHD, 61 (6.2%) had chronic lung disease, 224 (22.9%) had chronic gastrointestinal tract disease, and 437 44.6%) had pain syndromes (back pain, joint pain, headache).

All patients were investigated at three visits; complaints were evaluated on the first day of attendance at a medical institution, when physiological values (systolic and diastolic BP, pulse) were also determined and patients were screened for compliance with the inclusion criteria. Cortexin was prescribed for 10 days; 584 patients (59.6%) received 10 mg i.m. and 395 (40.4%) received 20 mg i.m.; doses were assigned randomly. The second visit, on day 10–14, was a telephone consultation to identify the presence/absence of clinical improvement and AE. At visit 3 (face-to-face), on day 30, changes in complaints and measures of the clinical picture were assessed. Patients carried out subjective assessments of treatment quality. Patients' status was assessed using an asthenia assessment scale (MFI-20), the Mini Mental State Examination (MMSE), and the Schulte test. All side effects and AE occurring during the treatment period were recorded in terms of frequency and nature and link with study drug.

Results were analyzed statistically in Statistica 10 (StatSoft Inc., USA) and Microsoft Excel, with computation of significance (p). Nonnormal distributions were analyzed using nonparametric analysis (the Mann–Whitney test was used for comparisons of pairs of independent groups in terms of ranking and quantitative characteristics). Results are presented as medians and 25% and 75% quartiles, Me[25%; 75%]. Differences with a first-order error probability of <5% were regarded as statistically significant ($p < 0.05$).

Results. Each day about five patients attended doctors with postcovid complaints (up to 30% of the entire out-patient neurology intake). About 2% of neurologists noted higher attendance rates – 6–10 per day. Among the most widely used drugs prescribed for correcting the sequelae of COVID-19 were antioxidants, B group vitamins, citicoline, antidepressants, and anxiolytics. All patients had asthenic disorders, decreased concentration of attention, fatigue, vertigo, sleep impairments, and irritability, typical of patients with any viral infection, though more severe in the first 12 weeks after the acute phase in the case of COVID-19. Patients were of the view that these symptoms were also observed at later stages and that the decreases in memory and concentration of attention did not develop immediately but were delayed in time, making it difficult to establish the connection with COVID-19.

The most frequent complaints were of decreased concentration of attention (100.0%), increased fatigue (97.5%), general weakness (93.7%), forgetfulness (92.4%), anxiety (89.9%), sleep impairments (81.7%), olfactory impairments (74.4%), vertigo (70.9%), irritability (69.6%), headache (69.6%), tinnitus (41.8%), feelings of fear (44.3%), tearfulness (38.0%) and others (breathlessness, pain syndromes, increased sweating, anosmia, hyposmia, dysosmia, paresthesia, hair loss, degradation of vision, BP instability, tachycardia, allergic reactions) (31.6%.). These complaints have also been noted in other studies [8, 9, 20]. In terms of clinical features, especially in elderly patients, postcovid mental impairments were identical to poststroke depression [21]. Impairment to neurotransmitter metabolism (insufficiency or, conversely, overproduction) results in disorganization of synaptic processes and is seen after virus infections and correlates with temporary memory impairment and decreased concentration of attention [19, 22].

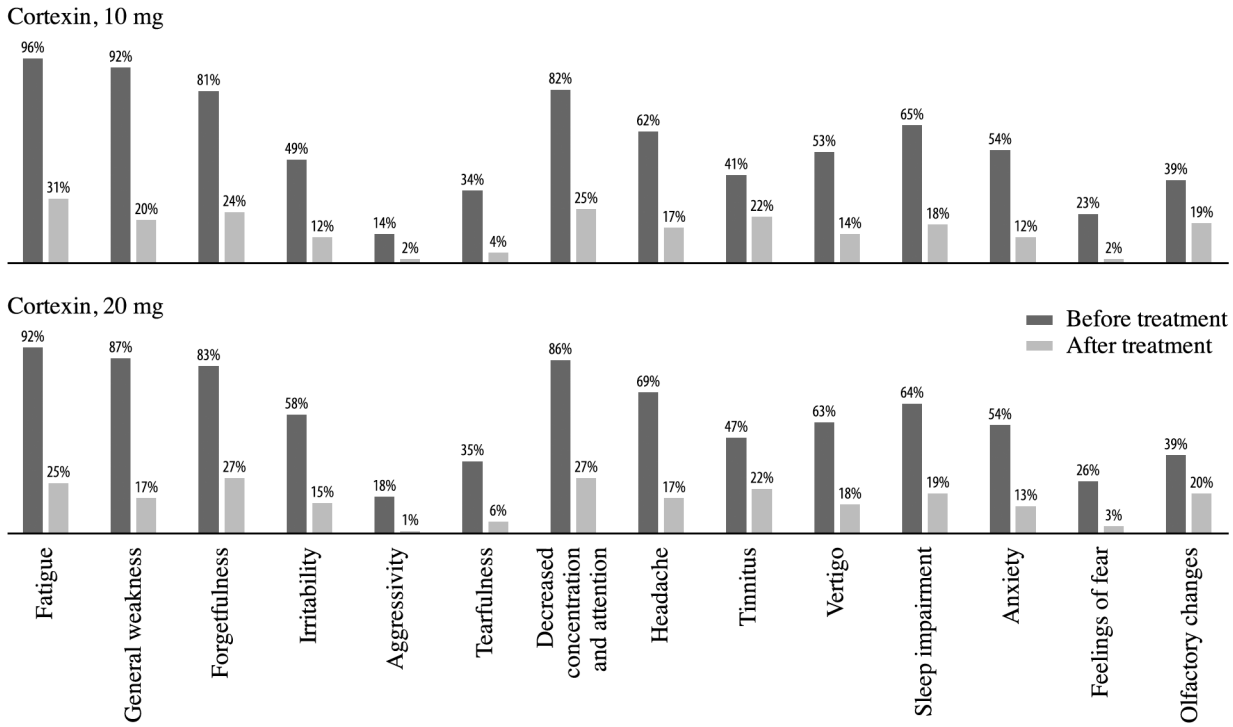

Fig. 2. Dynamics of complaints in study patients depending on Cortexin dose.

During telephone interviews at the second visit, all patients receiving different Cortexin doses noted improvements in their condition, with decreases in the severity or regression of complaints, and the absence of AE or side effects from treatment. All respondents confirmed further involvement in the observational program. The third visit allowed objectivization of the data obtained by telephone. All patients noted improvements in general condition, with increased physical and mental activity, and improvements in work capacity, regardless of Cortexin dose (Fig. 2). In patients receiving Cortexin 10 mg, fatigue decreased almost three-fold ($p < 0.001$) and general weakness by a factor of 4.6 ($p = 0.004$). Patients receiving Cortexin 20 mg showed more marked changes: fatigue decreased by a factor of 3.6 ($p < 0.001$) and general weakness by a factor of 5.1 ($p << 0.001$). Headache, vertigo, and tinnitus, which are difficult to evaluate as manifestations of PCS alone, also regressed in most patients and did not appear after one month of treatment ($p < 0.001$). Diagnosis and correction of such states is important, as they are common complaints decreasing patients' quality of life and treatment compliance [23].

Given that 74% patients with PCS complained of olfactory impairments, the investigations separately evaluated changes in these complaints. The following results were obtained: treatment was followed in both groups by two-fold decreases in olfactory impairments ($p < 0.001$). Use of neurotrophic factors can probably "spare" degenerating neurons and stimulate axon and dendrite growth and form new connections after viral infection [18, 24, 25].

The antianxiety, antidepressant, and anxiolytic actions of Cortexin were apparent by the second visit and persisted to the third, though in previous publications on the treatment of patients with chronic cerebral ischemia these effects were noted only on prescription of repeat treatment courses [26].

The use of Cortexin at different doses led to statistically significant correction of cognitive impairments and decreases in the severity of asthenia independently of the duration of the treatment of PCS (see Table 1). Marked improvements in terms of asthenia and cognitive status were seen in all patients, with greater effects in patients receiving 20 mg Cortexin (Fig. 3). Positive effects were seen from the initiation of treatment after COVID-19.

All patients evaluated treatment efficacy as high in terms of measures of subjective treatment quality assessment scales. No cases of therapeutic interactions between Cortex and other drugs used by study patients were seen, nor any AE.

Conclusions. This multicenter clinical and epidemiological program confirmed data on the high prevalence of postcovid syndrome and the significant variability of the clinical picture with a predominance of asthenic disorders. No significant correlation was found between clinical symptomatology and the severity of COVID-19, the percentage of lung tissue affected, or different times after the acute phase. The efficacy of Cortexin was demonstrated in correcting asthenic and cognitive symptoms in patients with PCS. The efficacy of both Cortexin doses was apparent by

TABLE 1. Treatment Results from Study Patients Depending on Time from Developing COVID-19

Scale	1–3 months	4–6 months	7–9 months	10–12 months
MFI-20, points				
Visit 1	61.0 [51.0; 69.0]	60.0 [49.5; 68.0]	61.0 [53.0; 68.0]	59.5 [53.0; 68.0]
Visit 3	42.0 [27.0; 51.0]*	42.0 [29.0; 54.5]*	38.0 [25.0; 54.0]*	31.5 [24.0; 54.0]*
MMSE, points				
Visit 1	27.0 [25.0; 28.0]	26.0 [25.0; 28.0]	26.0 [25.0; 27.0]	26.0 [24.0; 27.0]
Visit 3	29.0 [28.0; 30.0]*	29.0 [28.0; 30.0]*	29.0 [28.0; 30.0]*	29.0 [28.0; 30.0]*
Schulte test (sec)				
Visit 1	47.0 [36.0; 60.0]	46.0 [36.0; 60.0]	50.0 [40.0; 60.0]	45.0 [40.0; 60.0]
Visit 3	35.0 [30.0; 45.0]*	34.0 [29.0; 45.0]*	35.0 [30.0; 45.0]*	30.0 [29.0; 43.0]*

* Statistically significant differences compared with baseline level, $p < 0.05$ (Wilcoxon test).

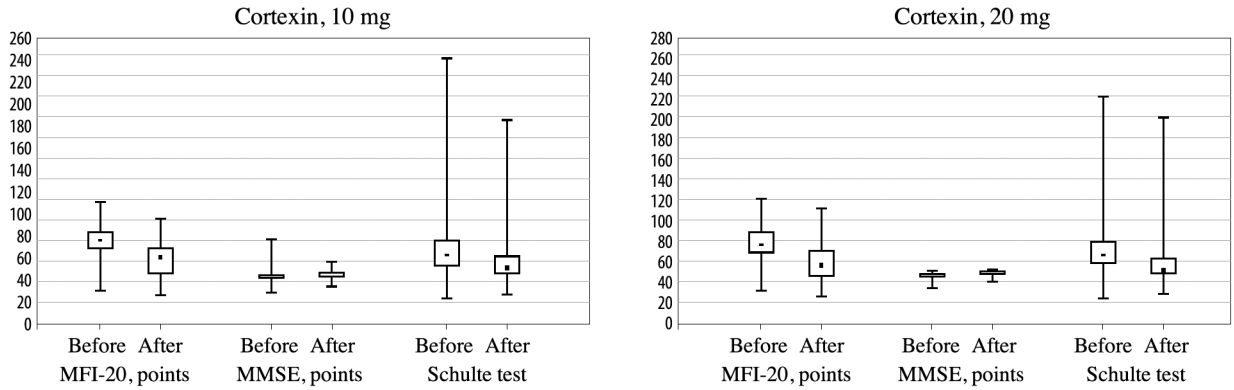

Fig. 3. Dynamics of patients' status depending on Cortexin dose.

treatment day 10–14 and persisted to one month. During the observation period, none of the patients showed any AE or unfavorable therapeutic interactions with other drugs. Cortexin had a dose-dependent effect in relation to asthenic and anxious-depressive disorders but not cognitive impairments. The high efficacy of Cortexin in relation to correcting cognitive impairments and asthenia, the presence of anxiolytic effects, the absence of side effects, and the compatibility with other drugs provide grounds for considering the option of using it for the treatment of patients with PCS.

The authors declare no conflict of interest.

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