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Clinical Characteristics of Japanese Encephalitis in the Convalescence Stage and Residual Phenomena, by I. S. Glazunov, V. V. Kartasheva and P. M. Khvan

We studied more than 300 people who had been infected with Japanese encephalitis. In this report we will try to analyze the clinic of the convalescence period and residual phenomena, that is, those conditions which appear in the organism of a person after the acute period of illness.

There is little literature on this subject.

In our literature we encounter only one such report (P. M. Allperovich, Neuropathology and Psychiatry, No. 4, 1940). He studied 23 convalescents and only 8 were well.

Kaneko detected residual phenomena in 35 of 200 people. However, later works point to a greater percentage of residual phenomena (Naka and Kuraiva - 46%, Sakurai and Ito - 63%).

It is understandable that a severe disease such as Japanese encephalitis cannot pass without a trace, leaving some type of pathological change in the organism of the person. Our detailed clinical and special laboratory studies are so interesting that it is desirable to direct the attention of doctors to this question.

In all convalescents, without exception, there were detected pathological changes of the nervous system (central) and internal organs. Our reports show that not all the patients come out of the acute period in the same manner. The various pathological deviations depend on the severity of the process. If some of the patients recover quickly, then others experience a more lengthy recovery period.

A very diverse chart is obtained during the neurological study of patients. We found changes in the motive, reflexive and perceptive spheres.

The greater changes were found in the mental spheres. Several of the disorders detected cause us to think of the irreversibility of certain pathological symptoms. Almost all the patients of Japanese encephalitis possessed numerous autonomic displacements.

Our studies lead us to disbelieve that the convalescent is finally well. This is confirmed by the condition of the central nervous system, the chart of blood, spinal fluid and also the status of the somatical spheres.

In the first days after the temperature drop, a majority of the patients still remain in an unconscious status; they urinate under themselves and do not take food. For several days it is possible to detect rigidity of the occiput and an increased muscle tone. The recovery progresses slowly and some recover poorly. The most frequent and constant complaints at this time are: general weakness, stubborn headaches, dizziness, noises in the head, fading of memory and loss of appetite. Many patients are very inertly apathetic, lack initiative, especially to work. Only after a month or longer do the above gradually decrease or disappear.

In those cases where the period of recovery is longer, there are present asthenia, with great exhaustion, weakness, lowering of tone and low moods. Similar forms are advantageous grounds for the development of hypochondriacal-asthenical conditions, which are more difficult to treat. An asthenical condition occurring as an expressed dispersive toxic-infective action on the brain is much more severe.

Changes in the psychiatric sphere occur in 70% of the cases in an early

period of the convalescence. They are non-persistent and dynamic, rougher in the first 2 weeks. However, there are encountered severe courses; in 3 patients there was a chart of an intellectual defect.

Let us stop on the motive disturbances. There were no reports, in our material, of degenerative-atrophic paralysis of the muscles of the neck or the shoulder areas. This is explained by the pathological process. The areas most affected by Japanese encephalitis are the interbrain, especially the substantia nigra, optic chiasm, subchiasm region and in some cases the varolius bridge and the medulla oblongata. The process is characterized by an extensive diffusion. Also affected are the cortex and the subcortical nodules.

During tick encephalitis, as is known, the chief disturbances are those of the cells of the forward horn of the cervical section of the spinal cord. In the clinical chart the paralysis of the muscles of the shoulder areas and the neck are predominant - this is the main differential feature of Japanese and tick encephalitis.

We noted numerous neurological symptoms in all the convalescents.

Most often noted were the paresis of the 7th and 12th pairs of the brain nerves (20%) of a central type, but in 3 cases there was an unstable two-sided peripheral paralysis of the facial nerves and in 3 cases one-sided. In 6 cases there was a one-sided paralysis of the 12th pair, of a nuclear origin, with atrophy of the tongue muscles of the affected side. Disorders of the eye movement were rare and weakly expressed. Only in 2 cases did we note paresis of the upward movement and in 3 cases ptosis of the upper eyelid. There were noted nystagmus affections, irregularity of the pupils and eye aperture, lower-

ing of the light reaction of the pupils and insufficient convergence. In 5 cases we were able to note aphonia, dysarthria, without disturbance of the act of swallowing. During the acute period these patients witnessed bulbar disturbances.

Oto-laryngological study established a two-sided paresis of the soft palate in these cases.

Cerebral hemiparesis was noted in 5% of the cases; hemiplegia was not seen in our material, although Japanese authors list a small percentage (3-4) as a residual phenomenon. During convalescence many patients could not move, even though paralysis was absent. There were disorders in reading, writing, difficulty in pronouncing words, a sharp disturbance of the coordination of movement, shaking of the eyelids, tongue and fingers of an extended hand.

In one case, after the drop of the temperature, there was an anemia of the face and bradykinesia, which looked like parkinsonism after Economo encephalitis.

A typical chart of parkinsonism developed in another case after 2 months. In the acute period, in certain cases, there were observed a masklike face, bradykinesia, sometimes a forced smile and various forms of hyperkinesia, but these symptoms were transient and occurred irregularly later.

Japanese literature reports of single cases of parkinsonism. The material of Alperovich lists no cases of parkinsonism. Study of the reflector sphere disclosed aniso-reflection of the tendinous reflexes in 20%, an increase - 70%, lowering - 30%, absence of abdominal reflexes - 20%.

If clear meningeal symptoms were present in the severe period, then they were noted in the convalescent period. The most durative symptom was the Kernig symptom accompanied by constant headaches; in such cases the spinal fluid was

varied and its pressure was increased.

Of the sensory disorders there were noted peculiar pains, hyperesthesia of the skin; in 2 cases pain in the upper extremities caused us to think of thalamic syndrome. In later stages of the recovery there were noted: loss of weight, dryness and peeling of the skin, falling out of the hair, expansion of the pupils. A so-called autonomic dystonia was noted in 80%. Also present were Horner's symptom and a subfebrile temperature which was not explained by the status of the internal organs. There were single cases of weakness of the sphincter of the bladder and disturbance of the sweat glands.

Owing to the spasm of the vessels on the periphery, which was indicated also by capillaroscopy, there was observed a paleness of the skin integument; as a rule the pulse was very liable, blood pressure was decreased. The body temperature was held at low levels. In 15% of the cases there was bradycardia, in 55% - tachycardia and only in 30% did the pulse remain normal. The Ascher's symptom was positive in 75%. The electrocardiogram in 45% was typical for a post-infection myocarditis, in 25% for infarct and in 30% it was possible to note a great lability of the heart muscle.

Regarding the organ of sight, there were hemorrhages on the lower part of the eye, residual occurrences of edema, in certain cases - obstructive occurrences, sometimes neuritis of the optic nerve with a passing over to atrophy. It was often possible to note a disorder of the appetite, usually distortion.

Analysis of the spinal fluid and blood in the period of convalescence revealed numerous characteristic peculiarities. The fluid is always colorless and transparent; formations of pellicle and netting were not observed. The quantity of albumen in 97.5% of all inspected was increased; in a majority of

the cases (93.7%) the diapason of vibration was in the levels of 0.42 - 2°/oo. In contrast to the acute period, a greater saturation of the spinal fluid by albumen draws attention. The general content of albumen from 0.33 to 0.47°/oo was noted in 3.8% of the cases, from 0.42 to 0.50°/oo in 16.2%, from 0.51 to 0.75°/oo in 30%, from 0.76 to 1°/oo in 18.7%, from 1 to 2°/oo in 23.8%, and higher 2°/oo in 5% of the cases.

Globulin reactions of the spinal fluid were positive in all cases and their intensity compared with the quantity of albumen. Observing the dynamic variation of the albumen, we unceasingly noted its increase in a later stage of the infection. As an illustration of these variations we will set down a case history.

Patient K, 21 years old. Became ill 4 September 1946. Temperature rose suddenly to 38, nausea, vomiting. Entered the hospital 7 September 1946, complained of severe headaches, dizziness and weakness. Memory hazy. Answers questions reluctantly, with one word. Face is hyperemized, temperature 40.6.

Regarding the nervous system; irregularity of the vision, left eye aperture narrower than right. Right nasolabial fold somewhat smooth. Tendinous reflexes increased. Pathological reflexes absent. Muscle tone in extremities somewhat increased. Kernig's sign positive; expressed rigidity of the occipital muscles.

The temperature decreased 15 September, but the patient felt poorly until 6 October. He experienced headaches, dizzy spells, inability to walk alone; mental perception was low. Most of the time the patient was in bed in a half-sleep status, not showing any interest to eat or to the surroundings.

The patient three times underwent exploratory punctures.

Date	Day of illness	Albumen in ‰	Test Pandy's	Reaction Nonne-Apelt	Cytosis	Neutrophils	Lymphocytes
13 Sep	10th	0.75	++	+	126/3	51%	49%
19 Sep	16th	1.15	++++	+++	67/3	22%	76%
9 Oct	36th	1.18	++++	+++	76/3	8%	92%

Thus the quantity of albumen progressively increases in later stages of the illness, the globulin reactions are expressed more intensively, the cytosis is far from normal. Such growing displacements of the albumen status of the spinal fluid is observed in 97.5% of the cases. In a later period of the illness the albumen-cellular composition returns to normal. The quantity of formal elements in the spinal fluid is increased from 11/3 to 652/3 in 92.3% of the cases in the period of convalescence. Of this number the increase from 11/3 to 30/3 was observed in 21.8% of the cases, from 31/3 to 50/3 in 20.7%, from 100/3 to 300/3 in 21.3%, from 301/3 to 650/3 in 3.7% of cases.

Thus, in the convalescent period the quantity of cells is still significantly increased.

Studies of the volume of carbohydrate-salt established the pathological displacements of the biochemical equilibrium of the sugar and chlorous sodium and the lowering of the absolute content of these substances in the blood of a majority of the patients.

The coefficient of the penetrability of the blood-brain barrier was varied in 77.8% of the cases at the expense of a comparative hyperglycorrhachia. During so frequent an increase of the penetrability of the barrier for sugar, the absolute quantity of sugar in the cerebrospinal fluid was lowered to 24-39 milligram % in 35.5% of the cases, increased from 66 to 83 milligram % in 16%, in the remaining fluids (51.5%) the absolute content of sugar was normal. An

increase of sugar of the blood was not noted; hypoglycemia - a frequent occurrence in the subacute period; in 50% of the cases a decrease of the sugar reached 70-47 milligram %.

A decrease of the quantity of chlorous sodium in the blood to 327-300 milligram % was observed in 56.3% of the cases; a decrease to lower figures - only in certain cases. The biochemical balance between the NaCl of the spinal fluid and the blood was disrupted, the penetrability of the brain-blood barrier for this substance deviates from the normal in 74.0% of the cases; of this number the coefficient of penetrability was varied, increasing from 1.56 to 2 in 43.6% of the cases, decreasingly from 1.3 and lower in 31%.

The data obtained by us point to significant and lengthy pathological variations in the spinal fluid.

Thus, for example, Patient G recovered from Japanese encephalitis in August 1946. In March 1947 he complained of headaches, dizziness, sleeplessness and loss of memory. From a neurological status it was possible to note a light asymmetry of the nasolabial fold and aniso-reflexes in the upper and lower extremities.

Analysis on 24 March 1947 gave the following results: spinal fluid colorless, transparent, quantity of albumen 0.39<sup>o</sup>/oo; Pandy reaction ++; Nonne-Apelt reaction +; cytosis 28/3; quantity of sugar in the spinal fluid 97 milligram %, in blood - 113 milligram %, coefficient of penetrability 0.85; NaCl in the spinal fluid - 619 milligram %, in the blood - 343 milligram %, coefficient of penetrability 1.8.

Thus, the hemato-liquid coefficient of penetrability for sugar and

chlorous sodium, 8 weeks after the acute period, was sharply increased at the expense of hyperglycorrhachia and hyperchlorrhachia. Evidently the virus of Japanese encephalitis causes stable and deep variations of the brain-blood barrier and also of centers regulating the interchange of substances. The latter is the reason for disruption of the carbohydrate-salt interchange.

It is interesting to note that Prof. Smorodintsev and Drobeshvskaya detected great quantities of specific antibodies in the spinal fluid of convalescents. The antibodies, with success, reacted with the antibodies in reactions of tying the complements. A simultaneous quantitative titrating of the antibodies of the spinal fluid and blood of one and the same patient indicated a correlation of the antibodies of the spinal fluid and blood equal to 1:5 - 1:10. This indicates the great displacements of distribution of the antibodies because the normal correlation of antibodies in the spinal fluid and blood is 1:300. Evidently these antibodies, in excess, penetrate into the spinal fluid, owing to the disruption of the barrier functions.

The morphological chart of the blood indicated by a large quantity of material, that the normalizations of the general quantity of leukocytes and leukocytic formulas extend to 5-6 weeks and longer. In certain cases the leukocytes interchange with leukopenia. Cases of leukocytosis from 12,000 to 27,000 are encountered during all types of complications and are accompanied by neutrophiles with displacements counterclockwise to bacillary and even to immature forms. The red blood was not varied.

The most frequent complications of this period were pneumonia, chronic-

sepsis, hemorrhagic diathosis (blood in urine, appearances of hemorrhaging, hematoma in various sections of the body).

The functional disruptions of the motive and autonomic orders can last months, but all are subject to recovery. An especially stable symptom is a so-called infectious asthenia. Towards the outcome of 4-5 weeks, during the most advantageous period, the occurrences of general weakness disappear, the patients begin to gain weight, however, some neurological symptoms remain stable even after 2 months and longer (affection of the brain nerves, disruptions of reflector spheres, pyramid signs, pathological variations of the spinal fluid). In single cases, after 3-4 weeks' lapse from the acute period, there developed charts of post-infection psychosis which led the patient to a psychiatric hospital.

Our material points out the severe variations of the nervous system which take place during Japanese encephalitis. To explain this we conducted accurate tests of sectional material (this will be reported later). In one case in which the patient died of accidental reasons, we detected hemorrhages in the brain, in this number diapedetic types, residual inflammatory occurrences (lymphocytic and plasmatic infiltrate) and accumulations of astrocytic glia, in the centers of inflammation, also oligodendroglia and Hortega cells. Evidently, in the period of convalescence, in the nervous system there continues a process of healing.

Many doctors still have difficulty in determining when a patient is completely well because they are not well acquainted with the disease.

Our studies will help in the evaluation of the status of a patient, recovering from this infection. Our material covered cases from several days to a year and beyond the acute stage.