SOME CONTRIBUTIONS OF ROMANIAN MEDICAL SCHOOL IN THE TREATMENT OF NEUROSYPHILIS BEFORE THE DISCOVERY OF ANTIBIOTICS

S. GĂBREAN

Abstract: In the first decades of the XXth century, neurosyphilis was a frequently disease in the world, for which different types of treatments were experienced, for example drugs containing arsenic (Salvarsan and Neosalvarsan). These drugs were not 100% effective, especially in tertiary syphilis. In the years following the First World War, based on the observations that in some cases high fever is favorable in the treatment of syphilis, it was induced the malaria infection which determines a high and prolonged fever, at patients with late syphilis. The risk for the patients was acceptable because malaria could later be treated with quinine. We present some dates concerning the contributions of Ghe. Marinescu, M. Ciucu and their fellow-workers, who used paludotherapy and Salvarsan or Neosalvarsan as adjuvant therapy in treating neurosyphilis.

Key words: neurosyphilis, treatment, Romanian medical school

Syphilis is caused by the spirochaete Treponema pallidum, which is 5-15µm in length and less than 0.3µm in thickness. This organism is generally sexually transmitted through mucosal membranes or small lesions of the skin. T. pallidum can be observed by silver stain, immuno-fluorescence, with dark-field, phase-contrast or electron microscopy. In 1913, after centuries of discussions concerning syphilis, H. Noguchi, a Japanese scientist, demonstrated the presence of T. pallidum on sections from the brain obtained at the necropsy of a patient with progressive paralysis, proving that T. pallidum was the cause of the disease. Short time afterwards, in the same year, Gheorghe Marinescu together with his assistant I. Minea, confirm this discovery and identify T. pallidum not only on sections from necropsies but also, for the first time, on sections from small fragments of brain obtained by the surgeon I. Jianu from a patient with progressive paralysis.

The various manifestations of syphilis are time dependent. Acquired syphilis has four stages: primary, secondary, latent and tertiary. Neurosyphilis refers to a site of infection involving the central nervous system and may occur at any stage of syphilis. There are four clinical types of neurosyphilis: asymptomatic neurosyphilis, meningo-vascular syphilis, general paresis of the insane and tabes dorsalis. Before the treatment with antibiotics, neurosyphilis was observed in 25-35% of patients with syphilis. General paresis, also known as dementia paralytic is a severe manifestation of neurosyphilis, which occurs approximately 20-30 years after the...
initial infection with Treponema pallidum and represents a chronic progressive fronto-temporal meningo-encephalitis with especially psychiatric symptoms [6, 12].

Syphilis has been a major health problem since the XVIth century and was treated with some ineffective remedies (guaiacum, mercury and others) until the beginning of the XXth century, when treatments based on arsenic as Salvarsan (arsphenamine, developed in 1908 by S. Hata in the laboratory of Paul Ehrlich) and Neosalvarsan were used. Malario-therapy was used as treatment for neurosyphilis due to high prolonged fever (a form of pyreto-therapy), an acceptable risk because the malaria could later be treated with quinine. For discovering the treatment of dementia paralytica by malaria inoculation (1917), J.Wagner-Jauregg was awarded with The Nobel Prize for Medicine in 1927. Malariotherapy was followed by either Salvarsan or Neosalvarsan as adjuvant therapy [1, 10].

In our country, a number of medical personalities showed interest for the treatment of syphilis: Gh. Marinescu, C. Levaditi, M. Ciucă, C. I. Urechia, Elena Puşcaru-Densusianu and their co-workers.

At the beginnings of Romanian medical education, the first reference concerning syphilis prevention was made by Carol Davila in his doctoral thesis sustained on 23 February 1853, thesis which was entitled “Syphilis prophylaxis” [3].

Gh. Marinescu was one of the first physicians in the world who received (1910) from Ehrlich the small doses of Salvarsan, which he managed to prepare in order to be tested in the great hospitals of the world [9]. If Salvarsan produced healing in some forms of syphilis (skin syphilis, for example), in neurosyphilis (tabes, general paresis) it gave no results. Gh. Marinescu tried to introduce Neosalvarsan into the body not by intramuscular or intravenous injections, but directly into the spinal canal or brain. He asked a former student, surgeon Ion Jianu, to do some small trepanations of the skull (it has to be mentioned that I. Jianu had never before worked on living brain); using these entries, Gh. Marinescu injected Neosalvarsan directly into the brain of the patients with dementia paralytica, but he didn’t obtain good results.

As it was mentioned above, Treponema pallidum was identified in the brain of general paralytics in 1913 so, in 1910, Gh. Marinescu was only suspecting the presence of the spirochete in the brain of these patients. In order to destroy the spirochete, Marinescu introduces Neosalvarsan by intraspinal injections directly into the cerebrospinal fluid, but once again without the desired results, the drug being irritable and caustic for the nervous tissue. Together with his assistant I. Minea, Marinescu realized at the Pantelimon Hospital an original method of treatment for general paresis, which was based on injecting salvarsanized serum into the cerebrospinal fluid. The serum was obtained from patients with syphilis who were injected with an important quantity of Neosalvarsan. After a few hours, were taken 40-50 ml of blood from which the serum was obtained after coagulation; this serum contained both a very small dose of Salvarsan and the syphilis antitoxin produced by the organism. Injected to the patients with general paresis, this serum showed good results, even curative properties [5].
After two years, in 1912, two American physicians, Swift and Ellis publish the same method of treating neurosyphilis with salvarsanized serum. Although Ehrlich himself, the discoverer of Salvarsan, mentions at a medical congress held in Königsberg in 1913, the world priority of Marinescu’s researches regarding the intraspinal injection of the salvarsanized serum, the discovery is attributed to the two American physicians, who later recognized that the paternity of treatment was belonging to Gh. Marinescu. However, they were saying that they had “improved” the serum, improvement which meant putting into phials the salvarsanized serum and commercializing it worldwide. There were also disapproving opinions regarding the treatment with salvarsanized serum, being considered that “it is a complicated method, and if sometimes may have a more or less curative effect, it still does not represent a preferable treatment or a progress in the treatment of nervous syphilis” (C. I. Urechia) [12].

Fig. no.2. Constantin Levaditi (1874-1953)

Fig. no.3. Mihai Ciucă (1883-1969)

In the 1920s, Constantin Levaditi and Robert Sazerac introduced bismuth therapy. For the treatment of neurosyphilis, bismuth therapy was done as in the case of visceral or skin syphilis, taking into account possible accidents like stomatitis, intestinal problems, jaundice etc. Generally, bismuth drugs seemed to have good results. There were patients who reacted very well at this therapy and there were also cases in which the patients showed inability to tolerate the bismuth. As a consequence, it was preferred a combined treatment, based on alternating bismuth salts with Salvarsan [2, 7].

In Romania, the artificial infection with malaria (malariotherapy) was successfully used in the treatment of neurosyphilis. The method was simple and consisted in the intravenous or subcutaneous injection of blood taken from a patient presenting a malarial attack; on average, in 8-10 days, the patients had malarial attacks and after 10-12 attacks they were given quinine and Salvarsan.

The principle of treating neurosyphilis by impaludation was based on the high fever which, probably, nonspecifically inactivated T. pallidum and generated a complex neuro-immuno-endocrine defense and repair reaction of the body. Malariotherapy was performed at Socola Hospital in Iaşi under the direction of M. Ciucă, at the Psychiatry Clinic of the Faculty of Medicine in Cluj under Professor’s C.I. Urechia direction, at the Neurological Service of the Institut for Mental, Nervous and Endocrine Diseases from Bucarest [11].

A special attention should be accorded to the researches made at Socola Hospital, the second internationally acknowledged centre for pyretotherapy, after Horton centre from England. At first, only Plasmodium vivax was used in treating neurosyphilis, being considered relatively safe and easy to control by quinine. After a few years, in 1925, Plasmodium...
falciparum was used, first at Horton center and soon afterwards at Socola Hospital. The team working here under the direction of Professor M. Ciucă, general secretary of the International Commission of Malaria for the League of Nations (1928-1938) also used in its researches indigenous strains of Plasmodium malariae, thus having an important contribution to knowledge of the sporogonic cycle of malaria parasites [4,8].

C.I. Urechia recommended for the treatment of neurosyphilis pyretotherapy using intravenous injections with beer yeast, which were painless and induced the required high fever (39.6-41°C). The method was easily applicable and seemed to produce an important improvement, especially in the case of general paralysis [12].

A special interest for neurosyphilis also showed Elena Densusianu-Pușcariu (1875-1966), the first woman in the world professor at a clinic of ophthalmology. She had better established the share of syphilis in the etiology of ocular diseases and was one of the first authors in the world who concluded that malarialotherapy had no curative effect in the optic nerve syphilis [12].

From this short presentation, one may conclude that in a difficult socio-economic context, the Romanian medical school managed to come with important, even original contributions in the treatment of neurosyphilis until the discovery of antibiotics.

**Bibliography**


