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PATHOPHYSIOLOGICAL ASPECTS OF *TRICHINELLA* INFECTION IN MAN

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Summary. - *The author presents significant elements of the pathomechanism of general disorders resulting from trichinellosis. Moreover, the pathophysiology of the gastrointestinal phase is also outlined while special emphasis is put on disorders in the early stage of invasion, in the acute stage of the disease associated with other clinical symptoms, and disturbances after other clinical symptoms have subsided. The pathophysiology of muscle invasion deals also with the essential morphological changes within muscle fibers and with biochemical and bioelectric disturbances in muscle tissue. An outline of cardiopathophysiology in the course of trichinellosis is also presented.*

Riassunto (Aspetti patofisiologici dell'infezione da *Trichinella* nell'uomo). - *L'autore illustra gli elementi più significativi del meccanismo patologico dei disturbi generali che si manifestano nelle infezioni umane da* Trichinella. *Sottolinea inoltre la patofisiologia della fase gastrointestinale con particolare riguardo ai disturbi collegati con la prima fase dell'invasione, con la fase acuta della malattia associata con altri sintomi clinici e con le manifestazioni cliniche secondarie. La patofisiologia dell'invasione muscolare viene trattata con particolare riferimento alle modificazioni della morfologia all'interno delle fibre muscolari e alle alterazioni biochimiche e bioelettriche del tessuto muscolare. Viene inoltre trattata la cardiopatofisiologia durante il corso dell'infezione trichinellotica.*

Introduction

The pathophysiology of trichinellosis is a complex one and not completely known.

There are two generations of *T. spiralis* which are involved in the pathology of trichinellosis: the mature forms and the larvae, which migrate and anchor in the muscle, however, the appearance and duration of the clinical signs do not correlate exactly with the life cycle of the parasite. Both mature and larval forms of *Trichinella* secrete from the stichocytes, an active secretive antigen [1] which induces antibodies production and is a trigger for the chain of the immunologic process occuring in the host. The hypersensitive reactions play a leading role in the pathology of trichinellosis. One of the basic pathomechanisms involved at the acute stage of trichinellosis is the attachement of circulating antigen-antibody complexes at the surface of mast cells. With the participation of IgE antibodies, immediate type hypersensitivity mediators are released from mast cells, including first of all histamine, serotonine, SRS-A, PAF and EChF-A (eosinophil chemotactic factor of anaphylaxis). The released mediators include also vasoactive amines, in particular bradykinin, responsible for the main pathogenic effect during the first stage of the disease, first of all within the capillaries. The increased amount of liberated mediators results in a dramatic effect. Due to increased permeability of capillary vessels, the fluid, electrolytes and albumin as well as cellular elements are translocated from the vascular lumen to the surrounding tissues; small intravascular thrombi, extravasation and cells infiltration around the vessels appear, thus presenting a histopathologic picture of vasculitis. Independently of the basic role of immune phenomena, the migration of larvae, their enzymes, i.e. hyaluronidase, collagenases, peptidases and lipolytic enzymes may also cause additional damage of the vascular endothelium leading to microcirculation and haemorrhagic disorders.

Vasculitis is a leading pathogenic process at the acute stage of the disease and involves multiple organs: lungs, the heart muscle, the brain, the intestinal mucosa but mainly the skeletal muscles which are the predominant site of the pathologic process. The immune complexes, large amounts of accumulated serotonin, increased numbers and rapid desintegration of neutrophils, of higher content of catecholamines are the source of endogenous pyrogen, which acting via the thermoregulation centre in the hypothalamus, causes the rise in the body temperature.

The complex action of these factors is responsible for the appearance of the clinical signs: fever, periorbital oedema; haemorrhagies to conjunctivae, to nail beds and internal organs; muscular pains and neurologic manifestations. The simultaneous appearance of these signs also indicates their uniform mechanism (Figs 1-3).

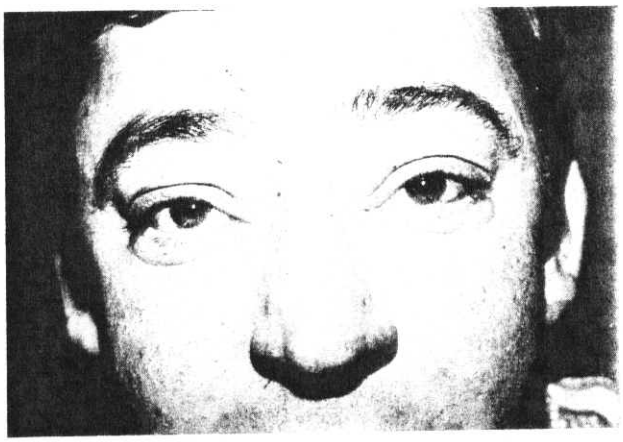

Fig. 1. - Periorbital oedema and conjunctivitis in patient in acute stage of moderate course of trichinellosis.

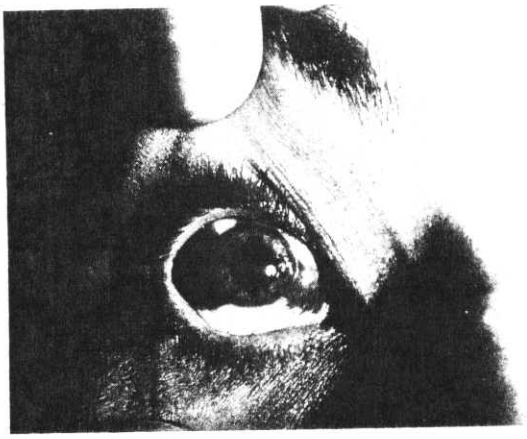

Fig. 2. - Haemorrhagies to conjunctivae in patient in acute stage of moderate course of trichinellosis.

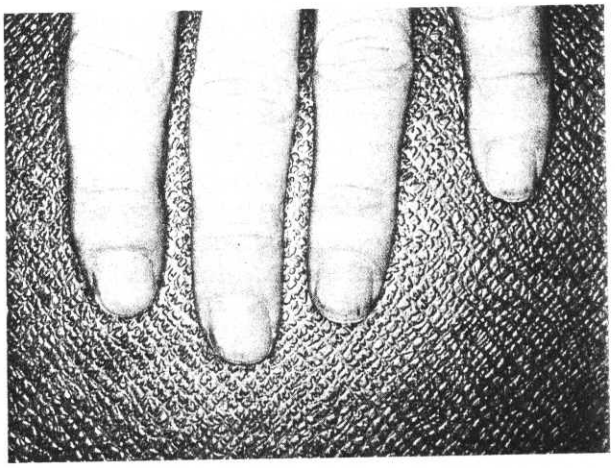

Fig. 3. - Haemorrhagies to the fingernail beds in patient in acute stage of moderate course of trichinellosis.

An increased number of eosinophils is an ever-present sign in trichinellosis. Eosinophilia is a very early sign of the disease, appearing in the first days of intestinal invasion and being induced by adult forms of *Trichinella* [2,3]. The augmented level of acidophilic granulocytes is thought to be induced by mast cell mediators but participations of complement, in particular its components C_5, C_6, C_7 or C_{5a} is also important. Thus, eosinophils are involved in the protective mechanism against *Trichinella* invasion. They are thought to be attracted to sites of the parasite invasion and the mediators released there. The role of eosinophils consists in direct damage to the parasite and degradation of the immediate type hypersensitivity reaction mediators, liberated by the mast cells [4, 5].

The majority of the host systems may be involved in the pathologic process of trichinellosis and therefore the principal changes occuring in the most important ones will be outlined.

Pathophysiology of the gastrointestinal phase

Intestinal trichinellosis is the essential phase of every *T. spiralis* invasion which determines further development and subsequent clinical pattern of the disease.

In the course of trichinellosis, alimentary disturbances may appear: a) at an early stage of invasion, preceding the typical syndrome of trichinellosis; b) at the acute stage of the disease, associated with other clinical symptoms; c) after other clinical symptoms have subsided. The intestinal disturbances result from immune, pathophysiological and pathomorphological factors. They result directly from *Trichinella* interaction with intestinal tissue as well as from action of metabolic excretory-secretory products of *Trichinella* intestinal forms. The early stage of the invasion involves first of all a few (2 to 4) days of diarrhoea and abdominal pains, reflecting the "self-cure" phenomena: the mature forms of *Trichinella* are expulsed from the intestine due to cellular infiltrates, including primarily lymphocytes B and mast cells, in the *lamina propria* [6]. Other authors are of the opinion that expulsion of *Trichinella* reflects activity of T cells [7].

Intestinal disturbances at the acute stage of trichinellosis or at the stage of protracted symptoms, independent of the immune background may result from pathophysiological or pathomorphological lesions. The former are reflected by altered absorption [8], disturbed motoric activity of the intestine (diarrhoea and constipation) and by the presence of cellular infiltrates within the lamina propria. Discussion on pathogenesis of trichinellosis cannot bypass the role of intestinal enzymes and hormones secreted by enterochromaffin cells at the base of Lieberkühn crypts. In particular, the role of vasoactive intestinal peptide (VIP) being released by mast cells has recently been stressed.

In part, this would explain the pathomechanism of diarrhoea in the course of trichinellosis. Even if the disturbances have not been fully appraised in patients with trichinellosis, results of experimental studies performed till now and demonstrating an impaired release of secretin during the intestinal phase of *T. spiralis* invasion [9, 10],

increased activity of lysozyme in serum and intestinal juice and stimulated activity of Paneth cells on the bottom of Lieberkühn crypts [11] have provided new data on gut pathophysiology in the course of intestinal trichinellosis.

Pathomorphology of intestinal mucosa in trichinellosis patients includes lesions of the epithelium, involving brush borders, lamina propria and smooth muscles of the gastrointestinal tract, deformation of villi, stimulated enterocyte proliferation at villi margins, Lieberkühn crypt hyperplasia, stimulated activity of Paneth cells and presence of massive cellular infiltrates in the mucosal sublayer. In the cellular infiltrates, mononuclear cells and plasma cells are also seen [12-14]. According to the authors the lesions may persist up to the 65th day after invasion (Fig. 4).

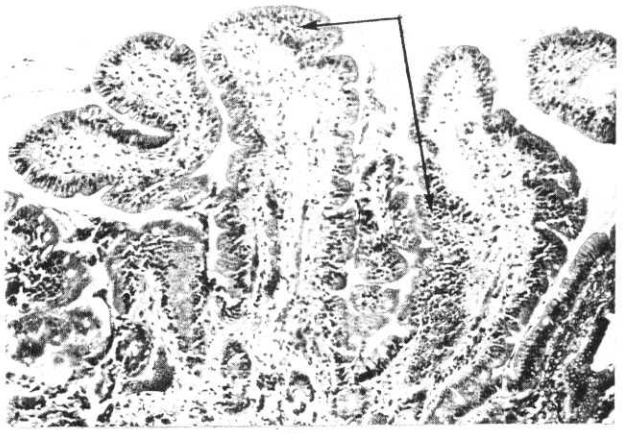

Fig. 4. - Jejunal mucosa in patient (33 years old) with mild course of trichinellosis with diarrhoea in acute stage of the disease. Biopsy was taken on 38th day of invasion and 21st day of clinical symptoms. Deformation of villi of the jejunal mucosa with proliferation of enterocytes on the side and infiltration of mononuclear cells and eosinophils in *lamina propria* are evident and indicated (HE staining, magnification x 40).

Pathophysiology of the muscle phase

Although the newborn larva of *Trichinella* will pass through or remain for short periods of time in a variety of cell types in the host, it is well established that the parasite will complete its development only in striated skeletal myofibers. During the growth and development in the muscle cells *T. spiralis* larva induces a variety of profound morphologic and ultrastructural, biochemical and functional alterations.

An increase in the amount of sarcoplasmic matrix, increase in size and number of nuclei and migration of nuclei from periphery to center of muscle fiber are very characteristic features. Increase in free ribosomes and intense proliferation of rough endoplasmic reticulum and smooth sarcoplasmic reticulum appear.

An intense proliferation of T-tubules and an increase in number of mitochondria and Golgii bodies were found increase in DNA and RNA content was noted.

Induction of such profound alteration in the trichinous myofiber suggests that the intracellular niche initially offered to the larva is unsuitable for its growth and development [15]. Thus, host myofibers invaded by *Trichinella* undergo a process transformation [16] or reorganization resulting in the formation of a chemically and structurally new type of host cell, the Nurse cell [17].

Cellular infiltration and angiomyositis appear, but they regress when the process of larvae encapsulation is finished.

The damage and increased permeability of muscle cell membranes results in the increased tissue-serum permition [18, 19]. This fact is proven both experimental and human trichinellosis for serum creatine phosphokinase (CPK), 1,6-diphosphofructoaldolase (1,6 ALD), aspartate aminotransferase (Aspat) and lactate dehydrogenase (LDH). Increase of CPK is the most characteristic feature in human trichinellosis. The percentage of high values between the 2nd and 5th weeks after onset amounted to 75-90 percent. The origin of increased serum CPK activity is clear as the enzyme is most specific. The increase of total serum LDH activity as well of LD_4 and LD_5 isoenzymes was noted in 50 percent of the patient in the early period of invasion i.e. between the 1st and the 6th week [20].

Bioelectric changes in the muscular tissue are also reflected by the pathologic electromyographic (EMG) tracing in the acute period of invasion [21, 22]. In patients with severe and moderate course of trichinellosis EMG tracing revealed primary muscle damage. This is not characteristic of trichinellosis, it only suggests the myogenous character of the functional changes. These changes disappeared within 2-3 months simultaneously with clinical improvement and regression of the muscular changes. During experimental infection in monkeys [23] the EMG pathological changes at first preceded the histopathological changes in muscles, but in the later period they correlated with the morphological alterations in the biopsy material (Fig. 5, 6).

Some EMG changes may be present 1-3 years after the acute trichinellosis, but no marked relation was noted between the character of the EMG tracing and the intensity of the invasion and histopathologic changes. However, these findings suggest that not all the muscular fibers regenerate, even after such a long period.

Cardiopathophysiology

T. spiralis larvae neither anchor nor encapsulate in the heart muscle tissue, however, their transitory stay in the heart tissue leads to some morphologic alterations. The nuclei of invaded myocardial fibers show an increase in both size and number, however, none of the other alterations in the structure or chemistry that occur in trichinous striated myofibers has been observed in myocardial fibers from the infected host. There are focal cellular infiltrations consisting mainly of eosinophils and mononuclears. These

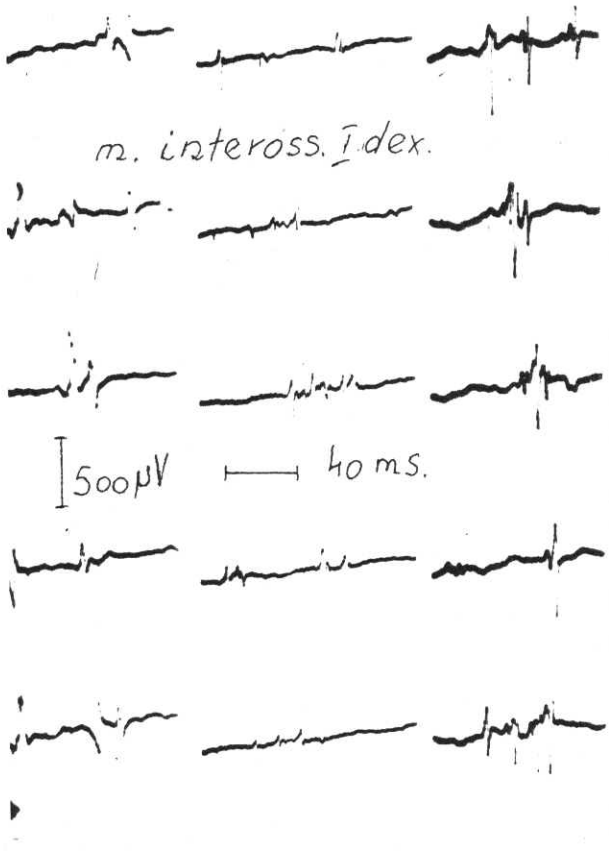

Fig. 5. - Electromyography in patient 42 years old in acute stage of severe course of trichinellosis: EMG tracing (during the rest) shows shortening of the duration of motor units potentials.

changes appear early and are more extensive in the later period, between the 4th and 8th weeks of infection. The picture is that of eosinophilic myocarditis with granulomas formation and often with proliferation of the connective tissue leading to interstitial myocarditis.

Electrocardiographic (ECG) changes in the acute stage of trichinellosis are due in some degree to metabolic disturbances mainly electrolytical ones. Deficiency of potassium ions in the heart muscle cells leads to polarization or depolarization disorders, manifested in the ECG

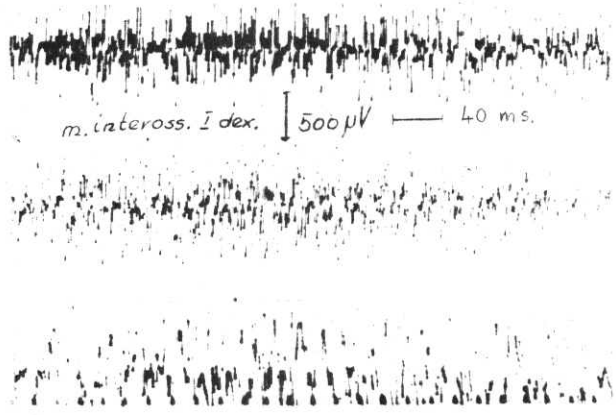

Fig. 6. - Electromyography in patient 42 years old in acute stage of severe course of trichinellosis: EMG tracing (during a maximal effort) shows the pathological interference.

tracing both in human and in experimental animals [24]. Compensation of potassium deficiency and normalization of serum level results in normalization of the ECG tracing.

Other metabolic disorders

The period of allergization and its symptomatology usually lasts for 2-3 weeks, then progresses stepwise to the later period characterized by protein deficiency and enzymatic changes. Hypoalbuminemia is probably due to progressive increases in the mass of *Trichinella* and their development and on the other hand to the coincident process of the reconstruction of the host tissues. Translocation of the albumin and fluids from the intravascular compartment to the interstitial space manifested by hydrostatic oedema and in the severe cases by transsudates into the body cavities. The degree of hypoalbuminemia corresponds with the severity of the clinical course. Hypocaliemia is often encountered and is usually linked with hypoalbuminemia. Although a moderate degree of liver enlargement is observed in some cases of trichinellosis, the serum level of specific liver enzymes remains unchanged [25].

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