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INTEGRATIVE CLINICAL PATHOPHYSIOLOGY – ALGORHYTHMIC DISEASE CONSIDERATION AND ETIOPATHOGENETIC CLUSTERS (EPC)

THE EPC OF THROMBOCYTOPENIA

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Summary

In order to upgrade the understanding of disease phenomena we have developed two methods, algorhythmic elaboration of disease pathways and etiopathogenetic clusters. Horizontal, vertical and longitudinal integration is driven by these methods. The pathways and networking of processes are crystallized out of plethora of clinical data (signs, symptoms, hidden dysfunctions, outcomes, etc) and knowledge of sub-systems (nano-molecular, thermal, macromolecular, genomic expression, cellular phenomena, etc.) acquired through reductionistic methodologies. Natural tendency to form the common crossing points of reactivity of heterogeneous pathways was noticed. The pathways converge and form etiopathogenetic clusters (EPC). EPCs integrate multiple inputs and multiple outputs. They look like natural integrators, the common „hubs"of human body response.

Algorhythms and EPCs may be considered as a counter-response to the real challenge - how to overcome the plethora of information and how to create well founded interpretation, both intellectually and cognitively. Clinical medicine and biomedical research are two major pillars for the integrative physiology of human body diseases/disorders. Information technologies have facilitated the usage of the pilling-up databases of verifiable information and myriads of new nano-scale relations. It may be stated that an understanding of postgenomic throughput methodologies and quantities of data is tantalizing challenge to medicine. And *vice versa*, potential clinical significance of molecular discoveries is, very often, yet to be investigated within the context of integral human physiology. Physicians' approach to whole body will always remain as the referent concept and orientation in medicine, despite a progressive compartmentalization into narrow fields of interest (specializations, sub-specializations). They may use algorhythms and EPCs as methodological attempts to fuse the visions and insights of the two cognitive pillars.

Platelet disorders and etiopathogenetic contribution within variety of diseases and conditions may be considered as unite of the pathophysiological processes. Thrombocytopenia, bleeding diathesis and hypercoagulability are outlined as the individual EPCs. On the other side, multiple pathways and networking of pathophysiological processes include platelet-related-events as chain component of natural networking within the disease states. The platelet counts and functional tests provide a valuable point-information relevant in clinical assessment of dynamics of given disease/state. Yet, "clinically-invisible" parts of platelet reactivity may contribute to the events in "remote" pathways and networking disease state. Three case studies are presented within the EPC of Thrombocytopenia.

Key words: Etiopathogenetic clusters, Algorhythmic elaboration, Thrombocytopenia, Compartmentalization of medicine, disease development

INTRODUCTORY REMARKS ON BIOMEDICAL RESEARCH AND CLINICAL PROSPECTIVE

Translational and gnoseological development of biomedicine has been burdened with multiple methodological obstacles and conceptual challenges. Postgenomic era continues to produce copious amounts of molecular insights into genomic, proteomic, epigenomic, transcriptomic (etc) dimensions of human body physiology and pathophysiology. In highly controlled simplified models well founded and reproducible interrelations are established. Elementary mechanisms are figured out. They contribute to refinement, reinforcement and reconfirmation of established concepts and visions, and sometimes to rejection of previous interpretations. Such perspective and visions, powered by information technology and statistical evaluation have set a stage for integrative consideration of pathobiological phenomena. Integration has become a tantalizing challenge of present era. Both physicians and bioscientists are faced with a paradox of surprisingly low practical usage of extensive knowledge of molecular omics-data. A part of problem is due to a nature of scientific research. Testing a validity of given hypothesis is based on classical scientific methods, which are reductionistic quantitative approaches. The simplified models enable appropriate controls, reproducibility, and ethically approvable investigation. Reducionistic approaches have been generating the knowledge of a type "more and more about less and less". On the other side, clinical medicine imposes demands of integral understanding of whole body reactivity. Disease manifestations have many facets related to body physiology disorders, psychological and emotional reactions, social relations, etc. Physicians' duty to act in appropriate time framework comes from a longitudinal dimension of disease processes. Natural propensities of disease development impose the limits for the optimal outcomes of medical interventions.

Understanding nosology (physiology of individual disease/disorders) requires, along with analytical consideration, the synthesis and testing the interpretation, daily, in each patient. Each patient-case study may be considered as re-testing step that may lead to consensual validation of given interpretation. The integral complex system reveals additional regulatory, interactive and networking phenomena unseen through simplified models of study. All reductionisitc analytical methods in medicine imported and adapted from chemistry, physics, biology, information technologies (etc.) have an inherent problem of simplification and methodological "ignorance" of complexities. On the other side, physicians are faced with complexities of integral approach. Physicians see pathophysiological processes as non-linear, complex and often redundant, containing a high degree of variability and not always predictable. The evaluation of a natural history of diseases and disorders in clinical reality and interventions are based on macro-scale knowledge and diagnostics. Understanding nosology (physiology of individual disease/ disorders) is not an easy task. Very often chiseling down the core nature of nosologic entities not-rarely reveals new dimensions. Evidence based medicine tries to enforce consideration of the nature of underlying pathophysiological processes. The strategy of «explicit, consciousness and judicious use of current best evidence» imposes immediate duty to improve practical and applicable knowledge at the heath-care level. Physicians are asked to integrate factual information, and semantic differences related to qualitative and quantitative approaches. Understanding etiology, dominant and parallel pathogenetic pathways, networking of processes, alteration of functional capacity of body functional systems and subsystems, multiple regulatory pathways (etc.) are components of individual nosologies. Integrative consideration includes multiple layers of body reactivity, including biological redundancy, inter-dependence on physiological gradients, and chronobiological alterations (etc.). Potential epistemological skewing is prevented through double blind randomized clinical studies which are designed, institutionalized and practiced in clinical research.

At the same time, students and practicing doctors and medical curricular systems, very much like scientists and research methodology, are inclined to limit their scope to the given narrow area of interest. They rush down into the limits of given branch medicine. Specializations and subspecializations are imposing professional limits of scope of interest. They solidify the system of compartmentalized medicine. Such narrowing of the specific area of interest comes from a natural tendency to reduce the complexity to a manageable simplicity. Compartmentalization of medical professions enables and increases the expertise level for the problems of the selected field. Such approach is relevant for the practical daily mastering of clinical problems of the patient. The flop side of compartmentalization is potential

underrepresentation of parallel systemic processes. Sometimes they are ignored and often seen just as a „noise in the system". However, systemic processes which go in parallel with localized component of disease may cause new pathways and complications in clinical course. It should not be ignored that >13% of hospitalized patients have been reported to developed multiple organ failure with no obvious expectation of such course [1].

ALGORHYTHMIC ELABORATION AS INTRODUCTION INTO THE INDEPENDENT LEARNING

Medical teaching/learning methods have been shaping novel pathways. Students are encouraged to become independent self-learners. They have at hands the portable self-accessible devices to dig out and to recall quickly relevant information. They receive less didactic instruction in form of classical teaching. Their navigation in the plethora of qualitative and quantitative information is increasingly facilitated by peer group interactions. Tutors are becoming the ancillary catalysers and supporters of self-growing of medical student. The tutors have reduced their pivotal role as principal source of relevant knowledge. Clinical and basic scientific insights in medicine are highly context-dependent. Thus case study approach may be considered as useful conceptual framework in that respect. Curricular reforms often emphasize that the students should be educated for a „lifetime of learning and change". The contents of teaching and learning outcomes are not to be based on unquestioned traditions or historic assumptions. The optimal self-learning procedure will instill the habit of independent learner with a critical usage and re-assessment of newly generated information.

Study of medical pathophysiology is a challenging task both for students of medicine, and their teachers. Optimal pathophysiological study includes vertical, horizontal and longitudinal integration of relevant knowledge and data. Vertical dimension refers to establishing causal relationships among clinical-macroscale signs, symptoms and dysfunctions down to the nano-scale of genomic expression, biochemical and biophysical reactions and cell physiology. It connects nano-scale world of molecular constituents with macroscale clinical manifestations of disease processes. Horizontal integration includes simultaneous processes that take place in neighboring and remote organs in parallel with the processes in primary affected organ. It clarifies relations of dominant etiopathogenetic pathway to parallel, secondary and/or conditioned ones. Longitudinal consideration refers to the temporal aspects of the disease that may have distinct manifestations, chain reactions; progressive functional degenerations (etc) depending on the time elapsed.

We developed method and published the problem solver book which brings didactically unique approach focused on etiology and pathogenesis of various diseases and disorders [2,3]. It contains inductive strategy that enforces the active role of the reader. The reader, instead of being a passive "consumer" of knowledge, becomes an active discoverer of relations, causalities and regulatory pathways. His/her active dealing with elements to be aligned into expected solutions, seems to be a key point for the efficient teaching/learning procedure. The method and book [4] systematically implements matrix-driven, problem-solving educational model, which consists of four steps**.**

Step 1: Exposition of chosen problem focused on underlying etiopathogenesis. The most often it is short presentation of "raw data" derived from patient disease history, diagnostic procedures, therapy, molecular insights, outcomes (etc.). Sometimes selected publications with experimental data are used as source, etc. Information is presented as abridged narratives and includes suitable tables and figures. Both quantitative (measured values) and qualitative information (e.g., description of symptoms) is included in the exposition. On average the exposition amounts one page and half, so it can be easily read through within less than ten minutes.

Step 2: Repetition of relevant knowledge is based on a multiple choice test. The statements are related to the exposition and referred teaching materials. The claims are written in a way to induce the most efficient scheme of learning studying. Namely, the correct answers are always written as a non-truthful statement, whereas the other four statements are truthful. Thus, just a reading through the repetitions corroborates a multiple facts related to the problem and student are led to re-call and re-fresh his/her relevant previous knowledge. Since individual statements describe heterogenic aspects of the exposed problem (relevant scientific data, established mechanisms in various experimental models, epidemiological remarks (etc), the repetition part is crucial for understanding and solidification of knowledge of the problem.

Step 3: Algorhythmic workout is graphic elaboration and representation of pathogenesis. It is active reconstruction and re-synthesis task in which students, out of pre-given 25-30 units of etiopathogenesis, build-up the cause-consequence sequence of events. It is simple inductive strategy of integration. He/she identifies dominant, contextual, parallel, and sequential etiopathogenetic pathways, as well as the branching points. Readers are asked to identify positive and negative feedback loops, and other regulatory pathways, as well as other relevant features of disease development and manifestation (Figure 1).

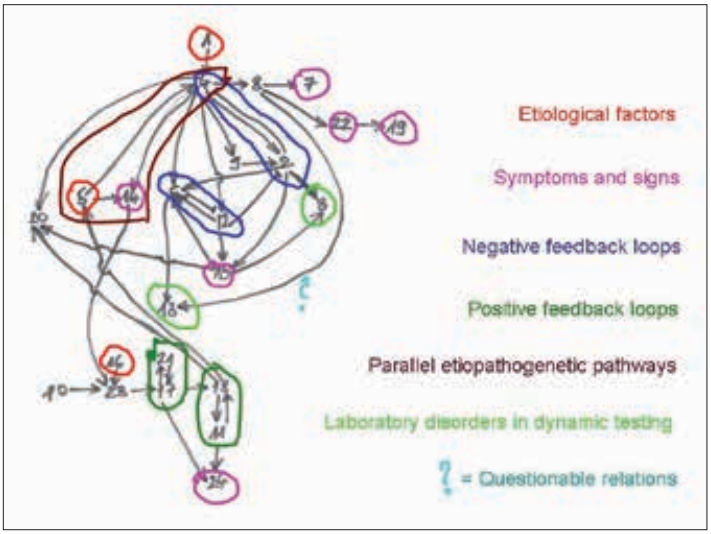

Figure 1. Integrative algorhythm graphic representation outlines interrelations among etiological events and clinical macro-scale manifestations. Regulatory loops and parallel pathways are easily identified and predictive testing may follow from understanding of underlying etiopathogenesis. (Arabic numerals are codes of the given etiopathogenetic elements interconnected by activating and/or inhibiting arrows – the gray basic mesh)

Step 4: Feedback integration of the problem deals with additional relations, systematization and quantitative aspects of the same problem. It gives some reiterative notions relevant for a proper understanding of underlying pathophysiology.

These four steps provide reiterative re-checking of understanding of multiple facets of etiopathogenesis. The reader is supposed to take an active role through solving the tasks and by construction of algorhythm out of given elements. Such graphic representation of etiopathogenetic processes is symbolic re-synthesis of knowledge. Etiopathogenetic algorhythms show natural ramifications and networking of disease processes. It provides a unifying framework to integrate biophysical, biochemical, morphological (and other) aspects of disease processes with clinical signs, symptoms and dysfunctions. A maximal insight into multiple aspects and facets of medical knowledge is given and enforced by four levels of problem elucidation. Detailed step-by-step problem solving leads readers to organize their thoughts and conceptualizations of etiopathogenesis in accordance with the contemporary theoretical and practical level of knowledge. It induces a solidified and reliable framework of disease processes. It was said that algorhythmic

method follows pathobiologic nature of disease and thus places the pathophysiology at the central position in a disease consideration. By effective utilization of both analysis and active re-synthesis of facts, concepts and visions, algothythmic pathophysiology has been praised as "the most effective study procedure" [7, 8]. The four layer driven active algorhythmic resynthesis does not ignore the context of events, since the problem solving is highly matrix dependent that serves as the bench-marks anchoring a disease reality [4] (Figure 2).

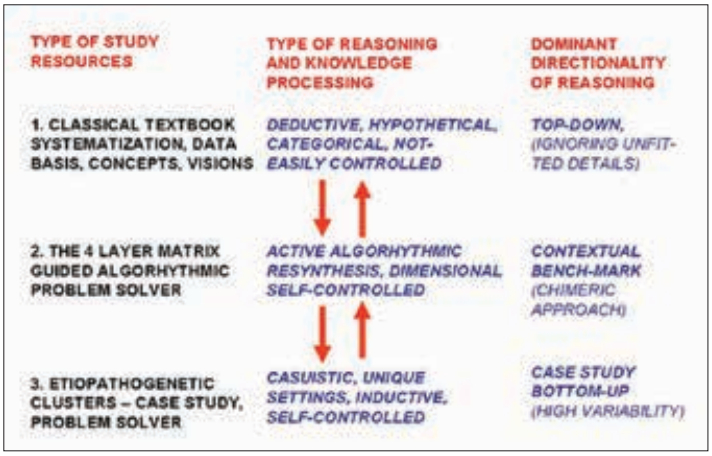

Figure 2. Three types of knowledge generation and processing according to the starting sources and study materials. Algorhythmic and clustering consideration of etiopathogenesis have enriched the study of pathophysiology with integral context, heterogeneous information resources and synthetic methodology which brings together qualitative and quantitative information/data both present in daily medical evaluation of patients' condition (indicated by red arrows).

NATURAL DISEASE PROCESS GROUPING AND NETWORKING – CASE STUDY APPROACH APPLIED TO THE ETIOPATHOGENETIC CLUSTERS

Example based learning has a power of immediate experience. It is a practical case study connected to a relevant frame of reference. It is traditionally considered as the most efficient method of learning. Patient practical case study makes intellectual, emotional and communicative impressions that facilitate in learner a long-lasting retainment of knowledge. Case-based learning in medicine enriches the clinical experience in diagnostics, procedural knowledge, therapy and abstract knowledge, as well. It is a continuous integral re-assessment of given data and knowledge. It

may be considered as fitting the patients' clinical reality and presentation within the context of theoretical considerations, taxonomic classifications, and referent knowledge (physics, chemistry, molecular biology, omics-sciences, etc). The algorhythmic approach to case based education has established a reliable bridge between the clinical macro-scale consideration and underlying nano-scale data derived from diagnostic and epidemiological procedures [5].

In addition, algorhythmic workouts of multiple problems tasks have revealed and interesting phenomenon of pathways' clustering. There is a natural tendency to form the common crossing points of heterogeneous etiopathogenetic pathways. The pathways converge and form etiopathogenetic clusters (EPC). EPCs integrate multiple inputs and multiple. They look like natural integrators, the common „hubs"of human body response. The EPCs receive negative (inhibitory) and positive (stimulatory) inputs, which are integrated within the EPC. They trigger new processes and pathways, and may induce secondary clusterings of pathways. The EPCs are spontaneously formed at various hierarchy levels of human body organizations. 1165 case studies were clustered around 91 EPCs in recently published book [6]. Het-

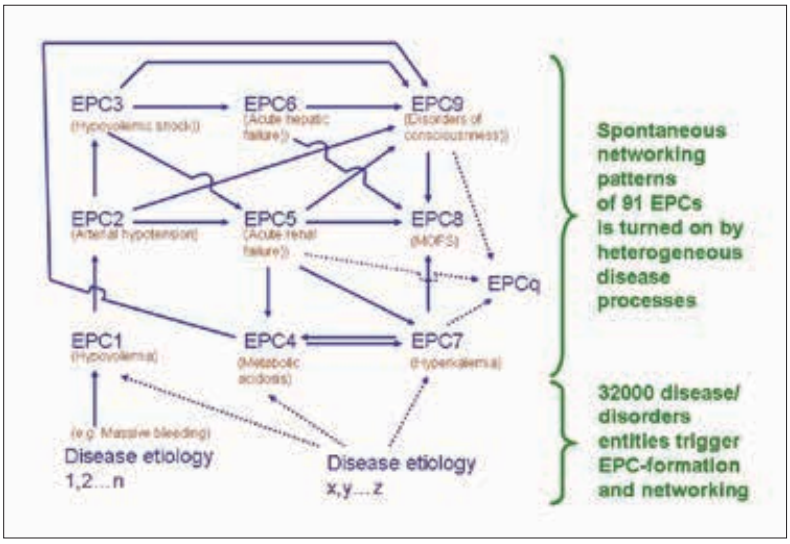

Figure 3. The EPCs are elements of spontaneous networking of events during disease development. Triggered by heterogeneous conditions (potentially 32000 diseases/disorders) 91 EPCs form patterns of human body pathobiological response. The example of networking induced by bleeding is outlined as group of interconnected EPCs. Involved EPCs are specified in parentheses - in red.
Abbreviations: EPC-etiopathogenetic cluster; n,x,y,z – any real number of 1-32000; q-any real number of 1-91.

erogeneous diseases "use" the EPCs as building elements in their development and progression (see Figure 3). Due to that, significant overlappings of symptoms, signs and dysfunctions in various conditions are.clinically manifested.

Those 91 EPCs can be grouped into following 12 levels: dyselecrolytemias, osmolality and fluid disorders, heat and temperature, acid-base disorders, macromolecular gradients disorders, cell energy and mass disorders, tissue hardening and mineralization, cellular-species disorders, organ dysfunction, functional system disorders, and multiple organ disorders [2,3]. Each study case is structured according standards practiced in medicine and they are enriched by the cutting edge information and up-to-date insights on relevant discoveries.

The EPC-case-based approach been described as "original contribution to understanding of pathobiological processes" [7]. These methods "from epistemiological point of view integrate qualitative and quantitative data" [7]. Bottom-up approach based on multiple case studies grouped together via the common clustering etiopathogenetic events. The problem solving is inductive casuistic with high natural variability (Figure 2) that nicely complements the categorical framework of conceptualization and general vision of classical study approach. It adds a multiplicity and variability of clinical reality. I was emphasized that " in each case study vertical, horizontal and longitudinal dimension of etiopathogenesis is promoted, and thus the integrative consideration has been imposed and maintained within the readers workout of the problem" [8]. Therefore, this approach has been praised to" stimulate and integration and digging out of pathophysiological foundations of clinical presentation and therapeutic intervention" [9]. The EPC-approach together with etiopathogenetic algorhythms promotes "the integration of clinical macro-scale and nano-scale world of molecules and forces" in daily practice and consideration of patients' conditions [5]. Therefore, the uniqueness of these methods was proclaimed as "the Zagreb model of etiopathogenesis consideration and confirmation" [10]. Professional bulletin "Liječničke novine" has, for more than one year, continued to offer contributions in various fields of pathophysiology in form of etiopathogenetic clusters and the solutions of the exposed problem.

PLATELET PATHOPHYSIOLOGY – THE ETIOPATHOGENETIC CLUSTER: THROMBOCYTOPENIA

Qualitative and quantitative disorders of platelet function contribute to pathogenesis of heterogeneous conditions [11]. In 91-EPC-system, platelet disorders as the primary etiopathogenetic events were described in patient cases within 5 EPC of ***Hypersplenism***, ***Tissue healing disorders***, ***Blood clotting diathesis***, ***Bleeding diathesis*** and ***Thrombocytopenia***. [6] In addition, platelet dysfunctions were present in some patients with other primary etiopathogenetic clusterings, such as EPCs of

Chronic liver failure, Acute liver failure, Ascites, Multiple organ failure, Sepsis, Autoimmunity, Graft versus host disease, Transfusion reactions, and ***Acute kidney failure.*** In these case studies platelet dysfunctions were present as parallel, secondary, tertiary (etc) events in disease networking.

Within the context of the symposium[1] the etiopathogenetic cluster Thrombocytopenia is presented. In Figure 3 introductory rosette of the cluster is presented. Each Arabic decimal code in eight fields corresponds with the contents of related study cases. In each study case after the exposition of clinical problem, the active solving of the problem is imposed.

The reader is supposed to figure out short etiopathogenetic algorhytm and systematization. Following the EPC-rosette three cases of thrombocytopenia are presented.

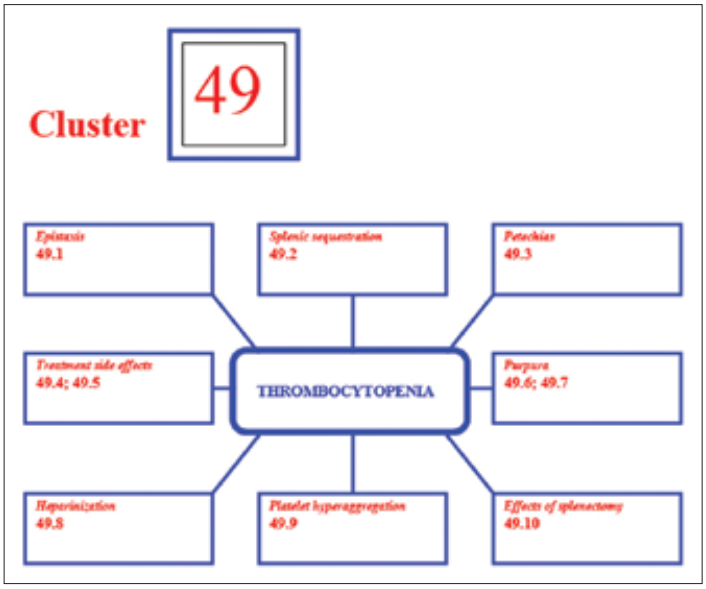

Figure 4. The EPC 49 – Thrombocytopenia is one out of 91 etiopathogenetic clusters outlined and elaborated in form of study cases in problem solver book (see Figure 3). For each case study the book provides itemized solutions, and it is convenient for self-education purposes. This EPC is of 23 EPCs within the Part Three of Clinical Pathophysiology [8].

CASE STUDY 49.5. ***Thrombocytopenia – with epistaxis and purpura in increased degradation of platelets as a consequence of taking quinine alkaloids***[2]

[1] The symposium on platelets held on March 12, 2015 at University of Rijeka.
[2] From Z Kovač et al. Clinical Pathophysiology. Etiopathogenetic clusters. Book Three. (Part Three) (in Croatian). Medicinska naklada, Zagreb 2013, pg 1213-14. It is in this text owing to courtesy and

The case study has been adopted from the article of Sigler E. et all, Lathyrism, Leg Cramps, and Thrombocytopenia: cascade of Events Starting in Concentration Camp. The Am J Med 2007; 120, e3.

I. Medical history. An 85-year-old Jewish woman from Romania has developed symptoms of purpura, and epistaxis. The laboratory determined thrombocytopenia ($2x10^9$ / L, normal range 150-400), and biopsy of bone marrow detected an increased number of megakaryocytic with normal hematopoiesis. The diagnosis of thrombocytopenia of unknown etiology was made. After treatment with platelet transfusion the number of platelets in the blood ($240\ x10^9$ / L) was normalized. In the few more occasions she had episodes of bleeding and thrombocytopenia, and after platelet transfusion the result was the repair of clinical symptoms and laboratory findings. From the medical history there were found out that during the Second World War and detention in a concentration camp, she was diagnosed with lathyrism. She occasionally used quinine for relief of leg cramps. The thromboagglutinin test result with quinine was positive, confirming the etiologic factor for thrombocytopenia. Stopping drug administration ceased the occurrence of thrombocytopenia for the following 8 years.

Additional insight: Lathyrism is a disease caused by prolonged consumption of legumes Lathyrus sativus, which contains toxic amino acid Beta-N-oxalyl-diaminopropionic acid (BOAA) which stimulates the glutamic acid receptors [12,13]. It appears in three forms: neurolathyrism, characterized by muscle weakness, convulsions and hypertonic paralysis, with a predisposition of affection of the lower extremities, and angiolathyrism (damage of the blood vessels) and osteolathyrism (damage of the bone growth) [14]. The disease was first mentioned 5000 years ago. in Ayurveda, and Hippocrates described the connection between eating L.sativus and appearance the neurological disorders 2000 years ago. Endemic in India and Ethiopia, and in Europe was recorded 1942nd years, in Vapniarci, the German concentration camp, when 800 Romanian Jews, who consumed bread made from flour listed plants, developed lathyrism.

The patient developed neurolathyrism, in the form of leg cramps, which is why she has been taking quinine.

Quinine is an extract of the bark of Cinchona pubencens, which grows in the Andes of Peru and Ecuador. As a remedy against malaria, in Europe it was brought by the Jesuits in the middle of 17th the century. It is often used to treat muscle spasms because it blocks sodium and potassium channels, thus slowing the traveling of action potential through the motor nerves, slowing depolarization and postponing

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repolarization, thus reducing the attractive forces between actin and myosin fibers and consequently reduces muscle contraction.

It is one of the most common cause of drug-induced thrombocytopenia, which in this case, usually occurs within 7 days from the start of the treatment. Side effects of quinine is a consequence of the immunological pathomechanisms with the formation of antibodies, immune complexes and binding to the membrane, and degradation of platelets (III.type of hypersensitivity), which leads to consumable type of secondary thrombocytopenia.

Thrombocytopenia impaired homeostasis of blood coagulation, which resulted in epistaxis and purpura in patient.

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorhythm of the disease)

1. The leg cramps
2. Increased number of megakaryocytic in the bone marrow
3. Purpura and epistaxis
4. Prolonged stimulation of the glutamate receptors and the development neurolathyrism
5. Taking quinine orally
6. The III. type of hypersensitivity, and damage of platelets
7. Eating legumes Lathyrus sativus
8. Reducing the number of platelets in peripheral blood

III. Classification, etiopathogenetic nature and features of disease/syndrome progression

According to information in this study case please list a) 3 features of etiology; b) 11 features of pathogenesis; c) 6 features belonging to chronobiology and processes distribution in the body and d) 5 features of clinical elaboration (diagnosis, treatment). The classification should be done by using the features specified on pages 661–2 of this book[2].

CASE STUDY 49.9. ***Thrombocytopenia – due to hyperaggregation*** **in thrombotic thrombocytopenic purpura in** ***pregnant woman with seizures*****, and fever, and** ***complete*** **abortion,** ***and lethal outcome*** [3]

[3] From Z Kovač et al. Clinical Pathophysiology. Etiopathogenetic clusters. Book Three. (Part Three) (in Croatian). Medicinska naklada, Zagreb 2013, pg 1218-19. It is in this text owing to courtesy and consent of Medicinska naklada-the Publisher, Editor-in-chief and author-dr Marija Šandrk. The solutions of the problem are provided at page 1639.

The case study has been adopted from the article of A. Sharma et al. Thrombotic thrombocytopenic purpura in a patient with very early pregnancy: clinical presentation and autopsy findings. Blood coagulate Fibrinolysis 2008, 19:727-30.

I. Medical history. A 25-year-old woman in the 5th week of pregnancy developed generalized tonic clonic convulsions and had vaginal bleeding. Before arriving at the hospital received three units of platelet transfusion and quinine antibiotics were ordained. On admission to hospital she was febrile, tachycardic (100/min, normal range 60-80), irritable and disoriented. The laboratory determined the hypohemoglobinaemia (60 g / L, normal range 120-160), thrombocytopenia ($6x10^9$ / L, normal range 150-400), reticulocytosis (27.6%, normal range 0.5-1), prolonged prothrombin time (16, normal range 10-14) and shortened partial thromboplastin time (26 s, normal range 30-45). There were found polychromasia, shistocytosis and erythroblastosis in the peripheral blood smear. Gynecological examination established the complete abortion (both abortion of embryo and the placenta, so that the uterine cavity was without disadvantaged parts of pregnancy). Contrast-enhanced computed tomography (CECT) scan of the head showed calcified granuloma in the left frontal lobe. Hemolytic anemia was set up as a working diagnosis and therapeutic plasma exchange was planed. However, the fourth day of the hospitalization, during the convulsive seizures, cardiac arrest has occurred and, despite of resuscitation, the patient died. Autopsy and histopathological examination showed the microthrombosis in the gray matter of the brain, kidney glomeruli, endocardium, liver, spleen and lymph nodes.

Additional insight: Thrombotic thrombocytopenic purpura (TTP, morbus Moschcowitz) belongs to a group of the thrombogenic microangiopathy, in which proper fragmentation of von Willebrand factor (VWC) is absent because of hereditary hypofunction of metalloenzyme ADAMTS 13 (ADAMATS is abbreviation according to engl. A disentegrin and metalloproteinase with thrombospodin-like domain) [15, 16]. Gene for ADAMTS 13 is located on chromosome 9q16, and is most pronounced in the hepatocytes and excreted protein binds to endothelial cells and megakariocite over thrombospondin receptors. Hypofunction of ADAMTS-13 and the formation of molecular assemblies of multimeric VWC and the endothelium, which strongly aggregates platelets and formed thrombus, which causes occlusion of blood vessels and ischemic dysfunction of the affected organs [17]. Renal failure, neurological disorders, purpura, hemolytic anemia, and fever appear as a consequence of above.

Other precipitating factors for TTP are some medications, autoimmune disease, pregnancy, and HIV infection. Infection with Escherichia coli 0157: H7 runs similar etiopathogenetic mechanism in the hemolytic-uremic syndrome.

Hemolytic anemia in patients is a consequence of mechanical hemolysis of the red blood cells in turbulent blood flow through areas with thrombus.

Increased number of reticulocytes in the blood (reticulocytosis) is an indicator of regenerative erythropoiesis.

Polychromasia is the presence of erythrocytes of different age levels, which was the response to hemolysis in patient. Erythroblastosis is a consequence of regenerative bone marrow response to anemia.

Fever in patients is a consequence of increased secretion of cytokines in response to the tissue microinfarctions.

Prothrombin time is used for the measurement of several coagulation factors (prothrombin, fibrinogen, factors V, VII and X), which is measured by the time it takes to create a plasma clot after the addition of thrombin [18].

Partial thromboplastic time test is based on the addition of phospholipids, the so-called partial thromboplastin, which replaces the platelets, and calcium, and is suitable for detecting defects of factor VIII.

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorhythm of the disease)

1. Neurological disorders
2. Hyperaggregation of platelets and thrombogenesis
3. Secretion of inflammatory cytokines and fever
4. Hemolytic anemia
5. Prolonged prothrombin time and shortened partial thromboplastin time
6. Obstruction of the blood vessels and microinfarction
7. Thrombocytopenia
8. Hereditary hypofunction of metalloenzyme ADAMTS 13

III. Classification, etiopathogenetic nature and features of disease/syndrome progression

According to information in this study case please list a) 1 features of etiology; b) 23 features of pathogenesis; c) 16 features belonging to chronobiology and processes distribution in the body and d) 11 features of clinical elaboration (diagnosis, treatment). The classification should be done by using the features specified on pages 1621-2 of this book.

CASE STUDY 49.3. ***Thrombocytopenia – with cutaneous bleeding successfully treated with autologous peripheral hematopoietic stem cell transplantation*** [4]

The case study has been adopted from the article of E.Elli et al. Successful treatment with T depleted autologous peripheral blood stem cell transplantation of refractory chronic autoimmune thrombocytopenic purpura. Haematologica 2007; 92: e7-e8.

I. Medical history. In September 2002 a 60 years old female patient was admitted due to mucosal and cutaneous bleeding, in particular nasal bleeding (epistaxis), gingival bleeding and diffuse pin-point cutaneous bleeding (petechiae) to arms and legs. Laboratory investigations showed only thrombocytopenia ($10x10^9$/l; normal range 158-424$x10^9$/l), without abnormalities in the peripheral blood smear. Family history, personal anamnesis and clinical status of the patient showed signs of other conditions, which could be associated with autoimmune or non-immune thrombocytopenia (drugs, HIV or Hepatitis C infection, other autoimmune disorders, malignancy). Physical examination did not reveal lymphadenopathy, or hepatosplenomegaly. Clinical diagnosis of autoimmune thrombocytopenia (AITP) had been done and confirmed with bone marrow biopsy. The patient was treated in the beginning with high dose glucocorticoid dexamethasone, with a partial and transient raise in thrombocytopenia ($50x10^9$/l). The splenectomy was done in December 2002, after high dose of immunoglobulin treatment. There was also only transient increase in platelet count. After that cytotoxic drugs were applied (cyclophosphamide, cyclosporine, azathioprine and vincristine), without effect. Therefore the patient had been submitted to T-cell-depleted autologous peripheral hematopoietic blood stem cell transplantation in September 2004. T-cell depletion from the transplant was done by CD34+ (hematopoietic stem cells specific superficial antigen) positive immunomagnetic selection. After the transplantation, the patient was treated with cytotoxic drug (immunosupressive) melphalan, granulocyte-colony stimulating factor (G-CSF; in order to stimulate hematopoietic recovery) and prophylactic antibiotics (fluoroquinolone antibiotic levofloxacine, co-trimoxazole, antifungal drug fluconazole, antiviral drug acyclovir). Hematopoietic recovery was observed 9 days after the transplantation (neutrophile count rise >$0.5x10^9$/l; normal range 1.5-7.8), and platelet count rise 18 days after the transplantation (>$20x10^9$/l). There were no major adverse effects of

4 From Z Kovač et al. Clinical Pathophysiology. Etiopathogenetic clusters. Book Three. (Part Three) (in Croatian). Medicinska naklada, Zagreb 2013, pg 1210-11. It is in this text owing to courtesy and consent of Medicinska naklada-the Publisher, Editor-in-chief and author-dr Ivica Horvatić. The solutions of the problem are provided at pages 1637.

the treatment nor severe infection. After a follow-up of two years the patient shows a stable platelet around $120x10^9$/l, and without need for additional treatment.

Additional insight: Thrombocytopenia is a decrease in peripheral blood platelet count. There are three groups of causes of thrombocytopenia: decreased formation of platelets (inherited or acquired bone marrow disorders, hematopoietic stem cell or megakaryocyte disorders respectively), increased destruction of platelets (congenital due to autoimmune reaction of the mother to fetal platelets or acquired) and increased separation of platelets in hypersplenism syndrome[18, 19]. Acquired causes of increased destruction of platelets can be immunological (increased destruction as a consequence of the reaction of the antibodies or other parts of immune system, whether idiopathic or induced by drugs or viral infections) and non-immunological (increased consumption of platelets in disseminated intravascular coagulation, thrombotic thrombocytopenic purpura or extensive blood vessels damage; direct viral effect) [20,21].

Autoimmune thrombocytopenia (AITP) is a disease of unknown etiology, caused by autoantibody to platelet membrane antigens (mostly membrane complex IIb-IIIa and Ib-IX glycoproteins) formation [19]. It occurs as acute form (most common in children after viral infections) or chronic form (more often in adults). Chronic AITP occurs as a single disorder or as a part of other autoimmune diseases (systemic lupus erythematosus) or malignant diseases (lymphoproliferative diseases). Autoantibody production stimulator is probably T-lymphocyte activity disorder (suppressive T-lymphocyte dysfunction or helper T-lymphocyte hyperactivity). Autoantibodies are of IgG class, and platelets lined with those antibodies become more susceptible to opsonization and phagocytosis mostly by splenic macrophages. In that way increased platelet degradation occurs. The disease is characterized by cutaneous (purpura) or mucosal (suggilation) bleedings. Cutaneous bleedings can be small pin-point (petechiae) or larger, hematoma (ecchimoses). The most important diagnostic criteria, besides thrombocytopenia, is increased number of megakaryocytes in bone marrow (important for differentiation from thrombocytopenias due to decreased formation of platelets) [22].

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorhythm of the disease)

1. Thrombocytopenia
2. B-lymphocyte stimulation
3. Petechiae
4. Suppressive and/or helper T-lymphocyte disorder

5. Autoantibodies to glycoprotein platelet receptors formation
6. Opsonization and increased platelet phagocytosis by splenic macrophages
7. Epistaxis
8. Increased megakaryocyte count in bone marrow

III. Classification, etiopathogenetic nature and features of disease/syndrome progression

According to information in this study case please list a) 3 features of etiology; b) 9 features of pathogenesis;c) 5 features belonging to chronobiology and processes distribution in the body and d) 14 features of clinical elaboration (diagnosis, treatment). The classification should be done by using the features specified on pages 1621-2 of this book[4].

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Sažetak

**Integrativna klinička patofiziologija - Algoritamska razradba bolesti i etiopatogenetski čvorovi.
Etiopatogeneski čvor Trombocitopenija**

U svrhu boljeg razumijevanja prirode bolesti razvili smo dvije metode, algoritamsku razradu putova bolesti i etiopatogenetske čvorove. Obje metode potiču horizontalno, vertikalno i longitudinalno objedinjavanje znanja. Informacije o putovima i mreženju patofizioloških procesa bolesti proizlaze iz mnoštva kliničkih podataka (znakovi, simptomi, prikrivene nedostatnosti, ishodi itd), te razumijevanja pod-sustava (nano-molekularna razina, termalni procesi, makromolekularne informacije, genomskoga izražaja, staničnih pojava, itd). Razumijevanje pod-sustava uglavnom proizlazi iz redukcionističkih pristupa. Postoji prirodna sklonost stvaranju križnih točaka reaktivnosti vrlo raznorodnih putova bolesti (EPC, prema engl. etiopathogenetic clusters). EPC integriraju mnoge ulaze i izlaze. Oni izgledaju poput prirodnih objedinitelja, čvorišnih„središnjica“, čovjekova tjelesnoga odgovora.

Algoritmski i EPC-pristup, metodički se mogu smatrati odgovorom na izazove rastuće pletore informacija i potrebe integracije znanja. Klinička medicina i biomedicinska bazična istraživanja dva su temeljna izvora integrativne fiziologije čovjekovih bolesti. Informacijske tehnologije olakšavaju korištenje rastuće količine provjerljivih podataka i velike množine nano-relacija. Razumijevanje postgenomskih masovnih integriranih tehnologija i količine podataka je pravi izazov medicini. I povratno, moguća klinička značajnost molekularnih otkrića se tek treba utvrditi u u kontekstu integralne fiziologije. Liječnikov cjeloviti pristup će uvijek biti referentni koncept i orijentacija u medicini, unatoč progresivnoj kompartmentalizaciji struka (specijalizacije, subspecijalizacije). Liječnicima su algoritmi i EPC važan metodički pristup za uvid i povezivanje oba stožerna izvora razumijevanja.

Trombocitni poremećaji i njihova etiopatogenetska uloga u raznovrstnim bolestima i stanjima može se smatrati temeljnom jedinicom patofizioloških procesa. Trombocitopenija, sklonost krvarenju, i hiperkoagulabilnoast krvi su zasebni EPC-ovi. S druge strane, multipli putovi i mreženje procesa uključuje trombocitna odstupanja kao lančanu komponentu prirodnoga širenja u bolesti. Brojnost trombocita i funkcijski testovi pružaju relevantnu informaciju za kliničku procjenu dinamike bolesti. Dodatno k tome, trombociti mogu bez zamjetljivih odstupanja sudjelovati u mreženju udaljenih fenomena bolesti. Tri su stanja u bolesnika predstavljena u EPC- trombocitopenija.

Ključne riječi: Etiopatogenetski čvorovi, algoritamsko proučavanje, trombocitopenija, kompartmentalizacija medicine, razvoj bolesti

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