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COMORBIDITY AND MULTIMORBIDITY IN MEDICINE TODAY: CHALLENGES AND OPPORTUNITIES FOR BRINGING SEPARATED BRANCHES OF MEDICINE CLOSER TO EACH OTHER

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SUMMARY

Comorbidity and multimorbidity represent one of the greatest chalenge to academic medicine. Many disorders are often comorbidly expressed in diverse combinations. In clinical practice comorbidity and multimorbidity are underrecognized, underdiagnosed, underestimated and undertreated. So that one can speak about comorbidity and multimorbidity anosognosia. Comorbidities and multimorbidities are indifferent to medical specializations, so the integrative and complementary medicine is an imperative in the both education and practice. Shifting the paradigm from vertical/mono-morbid interventions to comorbidity and multimorbidity approaches enhances effectiveness and efficiency of human resources utilization. Comorbidity and multimorbidity studies have been expected to be an impetus to research on the validity of current diagnostic systems as well as on establishing more effective and efficient treatment including individualized and personalized pharmacotherapy.

Key words: *comorbidity – multimorbidity - explanatory models - individualized and person-centered medicine*

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INTRODUCTION

The observation that some disorders and diseases occur together more frequently than it would be expected by chance is very intriguing. The simultaneous presence of multiple pathological conditions in the form of comorbidity and multimorbidity is more a rule than an exception in all populations of patients (Starfield 2006). There are many reasons why comorbidity is an important academic issue, not only in the context of complex pathphysiology and diagnostic classifications, overlapping clinical manifestations and pathogenesis, primary and secondary pathological processes, spectrum disorders and systemic diseases concepts, but also in the context of rational and creative pharmacotherapy, patient's self-management and health care utilisation, and drug development strategy. With regards to the global burden of diseases and high demands on healthcare systems atributable to comorbidity, there is an urgent need for better understanding the coexistence of various diseases in order to develop more effective and efficient prevention and treatment as well as to improve the well-being, work and social functioning and quality of life of patients in general.

Over the last several decades we have witnessed a steady accrual of a substantive body of knowledge in comorbidity medicine. Preventing, treating and managining comorbid or multimorbid conditions is one of the major challenges facing contemporary medicine and health care systems. Comorbidity medicine is closely associated with integrative and holistic medicine approach (Jakovljevic 2008) because comorbidities are indifferent to professional specialties and ever growing subspecialization in medicine.

DEFINITIONS OF COMORBIDITY AND MULTIMORBIDITY

Comorbidity can be defined in several different ways, and there is no consensus about it (see van der Acker et al. 1996). The construct comorbidity was introduced in medicine by Feinstein (1970) to denote the coexistence of two or more diseases, pathological conditions or "clinical entities" in the same patient. This definition includes „any clinically relevant phenomenon separate from the primary disease of interest that occurs while the patient is suffering from the primary disease, even if this secondary phenomenon does not qualify as a disease per se" (Feinstein 1970).

In general the term comorbidity has three meanings : 1. two or more medical conditions existing simultaneously but independently with each other; 2. two or more medical conditions existing simultaneously and interdependently with each other what means that one medical condition causes, is caused, or is otherwise related to another condition in the same individual; 3. two or more medical conditions existing simultaneously regardless of their casual relationship. Some authors define comorbidity as the simultaneous presence of two or more diseases in some individual which are associated with each other through pathogenetic mechanisms and more frequently than it would be expected by chance (the inevitable side) in contrast to multimorbidity which refers to the simultaneous presence of two or more diseases which appear randomly (the accidental side) not having any connection to each other through pathogenetic mechanisms (see Aragona 2009, Jakovljevic & Crncevic 2012). For Valderas et al. (2009) the term comorbidity refers to the

presence of additional diseases in relation to an index disease, while the term multimorbidity indicates the presence of multiple diseases in one individual. Starfiled (2006) suggests the term comorbidity for „the simultaneous presence of multiple health conditions when there is an index condition and other unrelated conditions", and „multimorbidity when no one condition is identified as an index condition". According to Grumbach (2003) the term comorbidity shoud be related to co-existence of two or more pathological conditions when one is predominant, while Goldberg (2011) thinks that „co-morbidity" is a term which might be better employed to refer to patients whose physical illness is accompanied by a mental disorder. There is also an interesting suggestion to use the term comorbidity for the co-occurance of two or more diseases, the term hypercomorbidity for the association of two or more diseases at a higher rate than expected by chance, and the term hypocomorbidity instead of the term anticomorbidity for diseases that appear together at a lower rate than expected.

EPIDEMIOLOGY OF COMORBIDITY AND MULTIMORBIDITY

Community and clinical population studies show that comorbidity is a common phenomenon, the rule rather than the exception, particularly in the elderly. It is commonly claimed that comorbidity or multimorbidity is a "normal state of affairs" for those aged over 65 years (Taylor et al. 2010). Although its prevalence rises with age, it is not a problem limited to the elderly population. The number of co-existing diseases also increases with age. However, the exact data are still missing. There is a far smaller number of studies on multimorbidity than on individual diseases epidemiology. According to some research comorbidity is reported in 35 to 80% of all ill people (Mezic & Saloum 2008, Bonavita & De Simone 2008, Taylor et al. 2010). The reported prevalence varies depending on the method of data collection, definition of comorbidity or multimorbidity and definition and the number of chronic conditions included in analysis (Frances et al-1990, Taylor et al. 2010). In the USA, aproximately 80% of Medicare spending is devoted to patients with 4 or more chronic illnesses, with costs increasing exponentially with higher multimorbidity (Wolf et al. 2002). A Canadian study showed that nearly 75% of obesity patients had comorbid diseases, mostly dyslipidemia, arterial hypertension and type 2 diabetes (Bruce et al. 2011). In a Russian study based on 3239 postmortem reports of patients admitted at multidisciplinary hospital for the treatment of chronic diseases, the comorbidity rate was 94.2%, mostly in combination of two and three diseases, and in 2.7% cases of 6 to 8 diseases simultaneously (see wikipedia). According to some literature reviews the rates of multimorbidity in the elderly vary from 49% to 99% with an average number of chronic diseases per person between 2.5 and 6.5 (Fortin et al. 2005). It seems that multimorbidity appears in an almost infinite number of variants with a generally low prevalence, which makes it difficult to get generalizable conclusions (van den Bussche et al. 2011). Triads of the six most prevalent individual chronic conditions (arterial hypertension, lipid metabolism disorders, diabetes mellitus, chronic ischemic heart disease, chronic low back pain, osteoarthritis) correspond to the multimorbidity spectrum of almost half of the multimorbid sample (van den Busche et al. 2011)

Mental disorders of all types are more common in patients with somatic illness compared with the general population. On the other side, somatic diseases are more common in psychiatric patients in comparison with general population (see Oreški et al. 2012). Patients with psychiatric disorders have also higher mortality rates in comparison with general population. The contribution of the somatic diseases to excess mortality has been inreasingly recognized, so, for example, chronic somatic diseases accounted for half of the excess mortality in patients with schizophrenia or bipolar disorder (Laursen et al. 2011).

TYPES OF COMORBIDITY AND MULTIMORBIDITY

Trying to understand th egeneral distribution and relationships of diseases in comorbidity, multimorbidity or polimorbidity is like researching a labyrinth full of possibilities because all diseases are more or less statistically associated with each other (see Schaefer et al. 2010). It is of great importance to recognize the underlying structure in the distribution and relationships of disease combinations. The term comorbidity refers to a multitude of different relationships among disorders and diseases.

Etiological and non-etiological comorbidity

Etiological comorbidity is related to concurrent damage to different organs and mind-body systems, which is caused by a singular pathological agent (e.g. due to chronic alcoholism, pathologies associated with smoking, systematic damage due to collagenoses) – (see wikipedia 2012). Epiphenomenal comorbidity refers to situations where several conditions are associated with one another, it is possible that one of them is just an epiphenomena or product of the other two (Agnold et al. 1999).

Primary and secondary disease comorbidity
(Feinstein 1970)

The question which condition will be regarded as the primary or index disease is not always self-evident.

There are three ways of making primary-secondary distinction: chronological sequence, causal inference (cause and effect) and symptomatic predominance (Klerman 1990). Patients with established diabetes who develop major depression may be very different from patients with major depression who later develop diabetes, while from cross-sectional perspective both are patients with diabetes-depression comorbidity (Valderas et al. 2009). The primary-secondary disease distinction has been generally used to signify cause and consequence between comorbid disorders.

Concurrent (co-occurring, simultaneous) and succesive (sequential) comorbidity

(Agnold et al. 1999)

The term comorbidity may include several temporal relationships, e.g. life-time comorbidity, simultaneous (intra-episode) and successive comorbidity. Concurrent comorbidity refers to the two disorders which run together, not only in time but in phenomenology (Agnold et al. 1999).

Casual and random comorbidity

(Schaefer et al. 2010)

Casual comorbidity describes disease clustering with a pathophysiological relation between the different diseases, e.g. shared risk factors. Cluster comorbidity indicates statistically significant associations between diseases without a casual explanation. Random comorbidity describes the co-occurrence of diseases by chance.

Undirectional and bidirectional comorbidity

Etiological and casual comorbidity may be undirectional or bidirectional. Direction of comorbidity may be defined as the ratio between the probability of each disease to onset before the other (Bonavita & de Simone 2008). For example, many patients with coeliac disease suffer from migraine but only a few individuals suffering from migraine are coeliac (see Bonavita & de Simone).

Complicated comorbidity

Appears as the result of the primary disease or its treatment, and usually subsequent after some time . Complicating comorbidity is illustrated by the case when one disease is caused by another disease and cannot be explained without its precursor (see Schaefer et al. 2010). Conjugated disease refers to the complication of the primary disease related to its etiological and pathogenetic factors (the cause of comorbidity). Iatrogenic comorbidity appears as complications which are negative effects of the treatment, for example tuberculostatic drug induced hepatitis, or corticosteroid induced osteoporosis in patients treated for a long time. Mental health medications certainly contribute to somatic comorbidity in individuals with mental disorders as well as somatic medications may induce mental disorders (see wikipedia 2012).

Trans-syndromal and trans-nosological comorbidity

Trans-syndromal comorbidity represents coexistence of two or more syndromes pathogenetically related to each other (see wikipedia 2012). Trans-nosological comorbidity denotes coexistence of two or more nosological units pathogenetically related to each other (see wikipedia 2012).

Diagnostic and prognostic comorbidity

Diagnostic comorbidity refers to an associated disease (whose)… manifestations can simulate those of the index disease, e.g. pneumonia and pulmonary infarction (see Valderas 2009). „Diagnostic comorbidity is likely whenever diagnostic criteria are based on patterns of symptoms that are individually nonspecific“ (Maser & Cloninger 1990). Prognostic comorbidity refers to diseases (in relation to an index disease) graded according to their anticipated effects on therapy and life expectancy (see Valderas 2009). Disorders that predisposes an individual to develop other disorders and complications have prognostic comorbidity (Maser & Cloninger 1990). Cogent prognostic comorbidity refers to comorbid ailments expected to impair a patient's long-term survival, e.g. recent severe stroke. Noncogent prognostic comorbidity includes other ailments, e.g. congestive heart failure or myocardial infarction more than 6 months old (see Valderas 2009).

Homotypic and heterotypic comorbidity

(Agnold et al. 1999, Valderas et al. 2009)

Homotypic comorbidity refers to disorders within a diagnostic grouping, e.g. major depression and dysthymia, bipolar disorder and cyclothymia. Homotypic comorbidity may be a marker of homotypic diseases continuity. Heterotypic comorbidity refers to disorders from different diagnostic groupings, e.g. major depression and conduct disorder, depression and cancer. Nonspecific symptoms may be an explanation for heterotopic comorbidity. Heterotopic comorbidity may be a marker of severity.

Concordant and discordant comorbidity

Concordant comorbidity refers to diseases as parts of the same pathophysiologic risk profile and more likely to share the same management and are more likely to be the focus of the same disease management plan (see Valderas 2009). For example, most adults with type 2

diabetes have at least 1 comorbid chronic disease, and 40% have 3 or more (see Kerr et al 2007). Concordant conditions may be either microvascular complications like retinopathy, nephropathy and neuropathy or macrovascular complications like coronary heart disease, cerebrovascular disease. Diabetes mellitus concordant conditions, such as arterial hypertension, heart disease, and retinopathy are parts of the same pathophysiologic risk profile and are more likely to be the part of diabetes disease management programs (see Kerr et al 2007). Discordant comorbidity refers to diseases that are not directly related in either pathogenesis or management and do not share an underlying predisposing factor, e.g. type 2 diabetes mellitus and irritable bowel syndrome or depression and rheumatoid arthritis.

Organic and non-organic comorbidity
(Samet et al. 2004)

Organic comorbidity indicates that an organic factor initiated and maintained the comorbid disturbance. In the non-organic comorbidity it cannot be established that an organic factor initiated and maintained the comorbid disturbance.

EXPLANATORY MODELS AND PATHWAYS TO COMORBIDITY AND MULTIMORBIDITY

Several different, but complementary models exist explaining why two or more diseases may occur together in one individual. Each model includes its own hypothesis about the etiology and patogenesis of the phenomenon and contributes to better diagnostics and more appropriate treatment. The method of multiple working hypotheses (see Oschman 2003) consists of „bringing up every rational explanation“ of comorbidity and multimorbidity phenomena, as well as of „developing every tenable hypothesis“ about them „as impartially as possible“.

Explanatory models

According to *the causation models* comorbidity can be explained by predispositions or consequences. *The antecedent model* proposes that one disorder contributes to etiopathogenesis of another one what can be mediated by various psychobiological and psychosocial factors. This model includes predisposing pathogenesis: one disorder or disease predisposes to another one. For example diabetes predisposes for coronoary heart disease. Anxiety disorder or depression predisposes to alcohol/substance abuse disorder. Two or more disorders may also predispose to each other, for example anxiety disorders, depression, alcoholism and other substance abuse disorders may be predisposition to each other. Major depression contributes to the etiology and progression of many somatic illnesses and this relationship may be mediated by immune, neuroendocrine and inflammatory factors as well as by behavioral factors like smoking, low physical activity, alcohol or drug abuse, diet, etc. (see Steptoe 2007). Specifically, major depression is claimed to be an independent risk factor for coronary heart disease. According to infornet theory, anxiety is a signal of behavioral alarm that there is a possible danger while depression is a signal that the desired goals are not achieved and helps disengage behavior from unatainable or inappropriate goals (Hyland 2010). Anxiety and depression are caused by outputs from a parallel as well as a sequential processing networks involving many different biochemicals. According to some opinions axis II disorders in DSM-IV also may predispose to axis I disorders. *The consequence model* suggests that one disease or disorder may arise as a result of another one or its treatment. Some mental disorders like depression may arise in some individuals with severe somatic disease like carcinoma or serious mental disorder like schizophrenia as an emotional response to diagnosis, treatment and the destruction of the future life prospects. Anxiety represents a large entrance to different mental and somatic pathology, while depression is a common response to various mental disorders and somatic diseases.

The common pathogenesis or the shared determinants models suggest that two or more diseases may have an overlapping pathogenesis. One underlying biological mechanism may contribute to two or more disorders, e.g. low serotonin disorders (anxiety disorders, depression, OCD, impulse control disorders). This model generally suggests common biological mediators, pleiotropic effects of the same genes, psychosocial adversities, psychological traits, emotional distress, and behavioral factors like alcohol and drug abuse, bad diet etc. which may lead to both mental disorders and somatic diseases (Weissman 2006, Steptoe 2007). The fact that one genotype can have multiple phenotype manifestations and on turn around a single phenotype may be the manifestation of multiple genes (Klerman 1990) as well as that two or more latent disorders may share a root cause (Borsboom et al. 2011) is very important when considering this model. The shared mechanism of comorbidity may be genetically determined, for example ion channel disfunctions can induce a brain hyperexcitability promoting both epilepsy and migraine, or acquired, for example when a head trauma leads to both epilepsy and migraine (Bonavita & de Simone 2008). *The associated risk factors model* indicates that the risk factors for one disease are correlated with the risk factors for another one making their simultaneous occurrence more likely, for example smoking and alcoholism are associated risk factors that increase the likelihood of chronic pulmonary obstructive disease and liver cirrhosis to occurr together (Valderas et al. 2009). In *the hetero-*

geneity risk factors model the risk factors for each disease are not correlated, but each one can cause either disease, e.g. smoking and age are indenpendent risk factors for lung cancer and coronary heart disease (Valderas et al. 2009). In *the independence model* the simultaneous presence of the diagnostic features of the two diseases is actually due to a third distinct disease, e.g. arterial hypertension and tension headache may be both related to pheochromocytoma (Valderas et al. 2009).

According to *the stress-diathesis or vulnerability-resilience model*, a genetic constellation and/or an early insult, predispose the patient to a series of later abnormal reactions and pathological conditions, so various somatic and mental disorders may appear after stressful life events or alostatic overload as pathological conditions expressing the shared diathesis. Diathesis and vulnerability refer to predisposition to disease or illness including constitutional, biological factors as well as psychological variables such as cognitive and interpersonal susceptibilities (Ingram & Price 2001). «Invulnerability», «resistance to disorder», «competence», «protective abilities», and «resilience» are terms indicating various degrees of opposite to vulnerability. Diathetic individuals may respond with abnormal or truly pathological reactions even to physiological stimuli which overactivate the physiologic system until the weakest part of it breaks down. At the most extreme vulnerability end of the continuum range, a small life stress is enough to result in a disorder whereas at the resilient end of the continuum range a great deal of stress will be necessary before disorder develops. In other words, with enough distress even the most resilient people will be at significant risk to develop a mental disorder or some somatic disease, although these symptoms will probably be milder than those of a vulnerable individual who experiences low to moderate stress, and will almost certainly be milder than those of the vulnerable individual under significant distress.

The developmental model or *the different stages of same disease model* suggests that one disorder may be just a developmental phase of the another one, e.g. generalized anxiety disorder commonly progresses to depression (the helplessness-hopelessness theory) as well as axis II disorders may be subclinical or attenuated forms of Axis I psychopathology (Klerman 1990). For time being, the multiaxial system is „agnostic“ regarding to possible a causative relationship for specific conditions in Axis I and Axis II (Klerman 1990).

The mixed disorders model and *the alternate manifestations model* in some cases may be an alternative to comorbidity and multimorbidity concepts (e.g. schizoaffective disorder or anxiety-depressive disorder instead of comorbidity of schizophrenia and bipolar disorder or comorbidity of anxiety and depression).

The multisystem diseases model may be also an alternative to the comorbidity concept in some cases. A multisystem disease is a disease that usually affects a number of psychophysiolologic systems, organs and tissues during its course. Some comorbid disorders interdependently related to each other may represent a multisystem disease or complex disorder. Many mental disorders and somatic diseases share a number of homonymous symptoms related to major neuropsycho-physiologic systems like energy producing system, central security and alarm system, sleep-wakefullness or rest-arousal system, neuroendocrine and imune stress-resilience (fight or flight) system, memory and learning systems, attachment system, reward-punishment system, etc. In association with these psychophysiologic systems it could be possible to understand comorbidity and multimorbidity better and create specific comorbidity modules.

The wrong diagnostics model when the comorbidity or multimorbidity is spurios or artefactual due to wrong diagnostic methodology (Valderas et al. 2009, Jakovljević & Crncevic 2012). It is important to have in mind a general tendency toward co-occurance, so that the presence of any disorder increases the odds of having almost any other disorder (Boyd et al. 1984).

Pathways to comorbidity

The conceptual basis of comorbidity rests on interconnections of mind, brain and body which interact and influence each other in both health and illness. The close interconnectedness of the mind, brain, neurotransmitters, endocrine, and immune systems suggests a unified inner healing system, self-aware and self-control organization. There has been linkage between repressive defenses, chronic helplessness and hopelessness, and dysfunction of the healing system (Dreher 2003).

Several pathways to etiological, casual or concordant comorbidity can be identified in the literatute: *shared predsiposition and vulnerability* (personality traits and types, joint genetic abnormalities), *shared risk factors* (stress, psychotrauma, food intolerance, unhealthy life styles, lack of social support, hostile thoughts, negative emotions, pesimism) and *shared mechanisms* (failed or unsuccessful coping, adjustment, resilience or defence mechanisms, endocrine and immune disruption, vital exhaustion, disruption of internal healing system).

Stress as a common factor in disease comorbidity

The role of distress and alostatic overload in the development of a wide variety of somatic diseases and mental disorders is well known. Increasing data indicate that stress activate not only hypotalamic-pituitary-adrenal axis, but also inflammatory cytokines and their signaling pathways, like nuclear factor kB (NFkB) both

in the periphery and in the brain (see Miller et al. 2008, Zeugmann et al. 2012). Stress induced proinflammatory cytokines in the brain significanly reduce the expression of brain-derived neurotrophic factor (BDNF), which play an important role in neuronal growth ane development, synaptic plasticity and, ultimately, mental disorders.

Risk personality types as a common factor in disease comorbidity

Some personality types (A,C,D) may be a common risk factor for multiple somatic disease and mental disorders. In the 1950s type A personality behavior was first suggested as a risk factor for heart disease, later for some other disorders. According to the current views, type A is characterized by three major features: 1. free-floating hostility so that minor incidents can trigger aggressive bahaviour, 2. time urgency and impatience associated with being hypersensitive, short-fused and easily exasperated, and 3. competitiveness with achievement-directed mentality experiencing high levels of stress (Friedman 1996). High-achieving and multi-task workaholics who push themselves with deadlines (with "try hard" and "hurry up" drivers) and cholerics (with "be perfect" and "be strong" drivers) who hate delays belong commonly to this personality type. Type C characterized with nonexpression of emotions, stoicism, and passive coping style, is a risk factor for cancer and less favourable survival outcome (Dreher 2003). Research in psychoneuroimmunology indicates that personality traits can be associated with deficits of the immune system portions capable for recognizing and eliminating cancer cells. Type D personality is prone to experience negative emotions and to inhibit self-expression in social interactions. Quite a number of studies have indicated type D or „distressed" personality as being a greater risk for multiple physical (heart disease) and psychological (depression, anxiety) health problems. If the individuial with type D personality cannot reframe hostile cognitions, and find way to creatively express negative emotions (anger, fear, sadness), he or she will be vulnerable to depression and heart disease, which are both breaking points. There is a strong evidence that both heart attack and depression are often preceded by vital exhaustion: extreme fatigue, irritability, and demoralization (see Dreher 2003).

„Shared endocrine-disruption" theoryof comorbidity

Environmental toxins, including substance abuse, negative interpersonal relationships, social isolation, etc. may be as detrimental as internal, genetically mediated, abnormalities (Nicolescu III & Hulvershorn 2010). A shared endocrine disruption induced by stress, food intolerance, chemicals, etc. may be a common mechanism in comorbidity. Recent evidence indicate that a variety of environmental endocrine disrupting chemicals (EDCs), like bisphenol-A, may be a common factor in multiple diseases including schizophrenia, obesity, heart disease, diabetes, thyroid disease, etc. (Brown 2009, Gruen & Blumberg 2009, Melzer et al. 2010). According to some data, more than 20% of the population in industrialized countries suffer from intolerance or food allergy (Zopf et al. 2009).

Allostatic overload and metabolic syndrome (MetSy) may be an important link between stress, endocrine disruption, inflammation and comorbidity (Jakovljevic et al. 2007), e.g. depression with cardiovascular diseases (Zahn et al. 2012) or cancer (Archer et al. 2012). It is interesting that metSy and insulin resistence may be associated with blunted central serotonin (5-HT) responsivity (see Jakovljevic et al. 2007). Autonomic nervous system imbalance is a consistent finding in the MetSy and various comorbidities (see Jakovljevic et al. 2007). Bidirectional association between metabolic syndrome and mental disorders, like depression has been demonstrated (Pan et al. 2012). Early detection and management of mental disorders among patients with MetSy and vice versa is strongly recommended.

Inflammation as a common mechanism in disease comorbidity

A low intensity inflamattion seems to be a common mechanism in multiple diseases including cardivascular disease, diabetes, cancer, depression, schizophrenia (see Miller et al. 2009). The activation of innate immune responses (inflammation) may contribute to the development of mental disorders in medically ill individuals as well as to the development of somatic disorders in mentally ill patients. It seems that l-tryptophan (TRP) metabolism may be associated with neuroinflammation. The kynurenine (KYN) pathway, a major tryptophan metabolic route operates as mechanism of defense against intracellular pathogens and as a mediator of stress response signals to the brain. Stress due to cortisol-induced activation of liver tryptophan-2,3-dioxygenase, which is a rate-limiting enzyme of TRP-KYN pathway, may induce disbalance between KYN (more than 95%) and serotonin (about 5%) metabolic pathway in favor of KYN (Oxenkrug 2013). This shunt of TRP metabolism away from 5-HT production towards KYN production induces 5-HT deficiency and consequently depression and other low serotonin syndrome disorders. Furthermore, KYN can be metabolized into kynurenic acid (KYNA) or quinolinic acid (QUIN). KYNA shows neuroprotective effects, while QUIN is excitotoxin involved in the pathogenesis of several major inflammatory neurological diseases and psychiatric disorders like stroke, Alzheimer disease, depression, etc (Leonhard & Myint 2006, Dantzer et al. 2011).

Human metabolic network topology (MNT) for disease comorbidity

Disease pathophysiology originates from a full or partial breakdown of physiological cellular and mental processes together with subsequant, often compen-

satory, interactions among components of the genome, proteome, metabolome, and the environment (see Lee et al.2008). A fundamental question in personalized cellular medicine related to comorbidity is to what degree the topological connectivity of cellular networks is related to the manifestation of human diseases, possibly leading to phenotypic interdependencies. It seems that "connected diseases show higher comorbidity than those that have no metabolic link between them; and the more connected a disease is in the MDN, the higher is its prevalence in population" (Lee et al. 2008).

Epigenetics of multimorbidity and comorbidity

We are not always victims of our genes, in many cases our genes are victims of us. Epigenetics suggests a novel pathophysiology and entirely new approach to prevention and treatment in the medicine of the 21st century, but the field is still in its infancy. The concept of epigenetic changes has added a new dimension to the study and our understanding of comorbidity and multimorbidity in psychosomatic medicine (. There are three basic molecular epigenetic mechanisms: DNA metilation, histone modification and microRNA dysregulation. DNA mutilation, associated with supression of gene transcription, and histone modification by acetylation, methylation, phosphorylation, and ubiquitylation have a powerfull control over the activation or repression of the associated genes (Sweat 2009, Hsieh & Eisch 2010). Histones are small basic proteins which, associate with each other to pack DNA into the nucleus. Hystones can be in one of two antagonistic forms, acetylated or deacetylated, and their equilibrium is regulated by the two enzymes, histone acetyltransferases – HAT, and histone deacetylase – HDAC (Zarate et al. 2006) Hystone acetylation is associated with increased gene expression, while hystones deacetylation results in repressed gene expression. Misregulation and aberant activities of HAT and HDAC, due to overexpression, mutation, translocation, and amplification, have all been implicated in oncogenesis, the loss of HAT and HDAC regulation has been involved in neuronal dysfunction and degeneration (Zarate et al. 2006). The conserved noncoding microRNAs (miRNAs) function in the cell to regulate gen expression at the posttranscriptional level as part of the RNA-induced silencing complex – RISC (Hebert 2009). Increassing evidence suggests that miRNAs are essential for the development and function of the brain and heart (Hebert 2009). Changes in a single miRNA may have profound effects on hundreds of target genes.

Epigenetic mechanisms play an important role in regulation of gene expression in response to environmental signals, drugs, and experience suggesting that epigenome resides at the interface of the genome and the environment (Sweat 2009). Some common disease like schizophrenia, bipolar disorder, depression, diabetes, cancer, coronary heart disease, etc. may be caused by epigenetic dysregulation of genes when no mutation is present. The enormous variation in disease incidence, predisposition, course, outcome as well as in comorbidities and multimorbidities may be due to epigenetic influences from actual events in the present, but also from those in the past. It seems that aging is accompanied by a substantial shift in epigenetic mechanisms, implying that diseases associated with aging, such as diabetes, coronary heart disease or Parkinson's disease, might be related to changes in epigenetic regulatory processes.

Changes in miRNA expression are reported in several diseases, such as cancer, major neurodegenerative disorders including Parkinson's disease, Huntingtonon's disease and Alzheimer's disease, and various heart pathologies including arrhythmia, cardiac fibrosis, angiogenesis, and cardiac hypertrophy (Hebert 2009). The underlying mechanisms of miRNA dysregulation in disease, and specifically in comorbidity and multimorbidity, are not yet clear. Changes in miRNA-regulated pathways may have an important role in apoptosis, lipid metabolism, and oxidative stress, and may directly or indirectly influence on disease-related genes, such as ACE and APOE. It is "an interesting hypothesis that changes in NFkB and/or YY1 may contribute, at least in part, to abnormal miR-29 expression in both heart and brain" (Hebert 2009). Changes in miRNA expression may have an impact on coexisting neurological, psychiatric and cardiovascular diseases by modulating organ function (brain and heart), accentuating cellular stress, and impinging on neuronal and heart cell survival (see Hebert 2009).

Epigenetic mechanisms are accessible therapeutic targets that are already in development for many diseases, including certain types of cancer, schizophrenia and Huntington's disease (Zarate et al. 2006). Regenerative therapy with stem cells for diabetes, heart failure disease, schizophrenia, dementia, Parkinson's disease, etc. is also a promising new area in epigenetic research. The epigenetic regulation of the stress response systems like the glucocorticoid receptor gene may be a molecular basis of a specific comorbidity and multimorbidity.

IMPORTANCE OF COMORBIDITY AND MULTIMORBIDITY

There are many reasons why the study of comorbidity and multimorbidity is of great importance for researchers, clinicians and health policy makers who are responsible for health care organization and funding. The failure to classify and analyze comorbid diseases has lead to many problems in medical statistics because comorbidity is strongly associated with the moment of detection, prognosis, treatment and health care outcome (Feinstein 1970, de Groot et al. 2003). Comorbidity is

very important for the aetiopatogenetic theories and diseases classification, prevention and treatment in modern medicine.

Importance for theory and research

Multimorbidity and comorbid disorders may have an important role in different types of research. They may act as a confounder, influencing the internal validity, or as an effect modifier, threatening the internal and external validity of the study (de Groot et al.2003). The studies of comorbidity contribute to more complex knowledge about factors predisposing, promoting, establishing and maintaining disease in patients with previously existing illness. They can lead to discoveries of new etiopathogenic concepts and models and related treatment strategies. Comorbidity studies have been expected to be an impetus to research on the validity of current diagnostic systems, particularly in psychiatry as well as on establishing more effective and efficient treatments within the concept of individualized and personalized pharmacotherapy. According to some opinions rules for clinical trials shoud mandate characterization of the subjects with regards to their total morbidity burden and patterns of types of illnesses (Starfield 2006).

Importance for treatment

Comorbidity and multimorbidity are associated with more complex clinical management, worse treatment outcome, and increase total healht care costs. Paying attention to comorbidity and multimorbidity may also contribute to more appropriate drug prescription and better treatment outcome in general. For example, arterial hypertension and allergic asthma are frequently comorbid with migraine. Beta-blockers are suggested as first choice in hypertensive patients with migraine, but in those affected by asthma they can precipitate bronchoconstriction (Bonavita & Simone 2008).

Comorbidities and multimorbidities are indifferent to medical specialties and highlight the intricacy and complexity of providing holistic understanding and health care, hence integrative and complementary medicine is an imperative in practice. Patients should be characterized by their morbidity burden as well as by the patterns of morbidity that they experience with time (Starfield 2006).

Importance for prevention

The comorbidity has significant implications for preventive medicine. If comorbidity is real, then prevention efforts shoud be comprehensive in their target, while an understanding of the nature of comorbidity will help better defining the targets of prevention. On-time interventions addressing shared risk factors should reduce the prevalence of various comorbidities. Unfortunately, prevention programs have usually operated in isolation from each other. Only integrative and comprehensive prevention activities can achieve a satisfying success.

Personalized and individualized psychosomatic medicine in practice

> *„Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals respond alike and behave alike under the abnormal conditions which we know as disease“ (William Osler)*

Comorbidity is an extremely important issue in personalized medicine in regards to the choice of medication, medication tapering, prediction and avoidance of unwanted side-effects, follow-up treatment and achieving full recovery (Jakovljević 2009, Jakovljevic et al. 2010). In patients with somatic disorders, comorbid mental disorders may 1. modify subjective reactions to somatic symptoms (amplification or diminution and neglection), 2. reduce motivation to care for somatic illness (demoralization), 3. lead to direct maladaptive physiological effects on bodily symptoms, and 4. reduce the ability to cope with somatic illness through limitation of energy, cognitive capacity, affect regulation, perception of shame or social stigma. On the other side, somatic comorbidity in psychiatric patients is associated with 1. shortened life-time because the mortality due to somatic diseases is higher in patients with major mental disorders than in the general population (Maj 2009), 2. more and severe adverse events during psychopharmacotherapy, 3. more treatment noncompliance and nonadherence, 4. lower quality of life and lower subjective and objective well-being in general.

The development of an appropriate integration between mental health and somatic health care is a crucial issue in psychosomatic medicine. The idea of achieving a personalized molecular medicine is a laudable goal, but there are multiple barriers to its implementation (Dean 2009). It is important to note that the concept of personalized psychosomatic medicine is extending beyond pharmacogenetics and pharmaco-genomics, particularly beyond contemporary treatment algorithms and it includes the consideration of all scientific information valid for the diagnosis of multiple diseases and their holistic and successful treatment. Generally speaking, mental disorders as well as somatic diseases develop as an interaction between stress and an individual's vulnerability to stress including genetic, epigenetic and acquired predispositions to mental and/or somatic disorders. The effect of early adverse life events (EALs) and a gene-environment interaction may play a role in the development of stress vulnerability (Zeugman et al. 2012) including risk factors for multi-

farious diseases .The theory of allostasis allows us to develope an integrated model of the interplay of context, history of EALs, current stressor exposure, internal regulation of mind-body processes, and comorbidity or multimorbidity through time. Personalized psychosomatic medicine is based on the hypothesis that each patient is a unique individual in health and disease, who should get highly specific and personally adjusted treatment for her or his comorbidities and multimorbidities including mental health protection and promotion. Although the history of psychiatric genetics is mainly a story of unreplicated discoveries and disappointed expectations, epigenetics offers a new hope to personalize psychosomatic medicine. Challenges for personalized psychosomatic medicine will include the technology of individual whole-genome sequencing and the concept that phenotype reflects a complex interaction of genes and the environment. Genetic and biomarker testing that are now on the horizon could improve objective assessments of disease, comorbidity and multimorbidity, disease severity and monitoring of treatment responses.

CONCLUSIONS

Over the last several decades we have witnessed a steady upsurge of a substantive body of knowledge in comorbidity medicine. Comorbidity and multimorbidity are challenging issues for researchers, clinicians and health policy makers. The high prevalence of comorbidity and multimorbidity have a significant impact on both positive responses to treatment and the occurrence of adverse events. Thus, the current narrow focus on single diseases should be replaced with a holistic view and approach to the patterns of comorbidity and multimorbidity in both academic and clinical medicine.

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