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Psychiatric manifestations of autoimmune diseases – diagnostic and therapeutic problems

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Summary

In autoimmune diseases, also called connective tissue diseases, many systems and organs are involved, including central, peripheral and autonomic nervous system. The frequency of neurological and neuropsychiatric manifestations varies in certain autoimmune diseases. One of the most common causes of these symptoms are vascular pathologies, including inflammatory and thrombotic, immunological and atherosclerotic changes. Neuropsychiatric complications may present as a single symptom or might form a syndrome. In a particular patient a form a syndrome might change in time presenting as a different syndrome. Quite a lot of these symptoms are not a result of a disease itself, but of its treatment, metabolic abnormalities, arterial hypertension or infection. Steroids play a particular role in the induction of these complications. The role of increasingly used biological agents is uncertain. The most frequent psychiatric manifestations of the connective tissue diseases are: benign behavioural changes, emotional instability and sleep impairment. Neuropsychiatric symptoms are most frequently seen in systemic lupus erythematosus (up to 80% of patients), particularly with the co-existent antiphospholipid syndrome. Psychosis with or without seizures are included in the diagnostic criteria of the disease.

A separate clinical problem is an induction of a synthesis of autoantiobodies by some drugs, including psychiatric drugs. These antibodies induce clinical symptoms of an autoimmune disease only in some patients, most frequently the symptoms of lupus erythematous, co called: drug induced lupus, including arthralgia, myalgia, fever, skin lesions and serositis. The diagnosis and treatment of psychiatric complications of autoimmune diseases is quite complicated. It is extremely important to distinguish whether a particular symptom is primary to the disease itself or secondary to its treatment. The most important recommendations are treatment of the underlying disease, its exacerbations and chronic phase, and prevention and treatment of vascular problems.

Keywords: neuropsychiatric symptoms, autoimmune disease

Introduction

Autoimmune diseases, also called connective tissue diseases, have multi-organ manifestations. The prevalence of neuropsychiatric symptoms differ and depend on the central, peripheral and autonomic nervous system involvement. The most common psychiatric manifestations of autoimmune diseases are the following: progressive

cognitive dysfunction, emotional instability, mood and sleep disorders, impaired memory, psychosensoric disorders, depersonalisation, derealisation, depression, anxiety, hallucinations, and delusions of reference. One of the reasons of the above disorders are vascular pathologies of multifactorial pathogenesis, mainly thrombo-inflammatory and immuno-inflammatory. The immunological pathogenic factors leading to vascular involvement are autoantibodies and proinflammatory cytokines [1]. It is also worth mentioning, that in patients with connective tissue diseases an accelerated atherosclerosis is associated with chronic inflammation and the presence of autoantibodies. The subclinical atherosclerotic lesions can be detected in 30% to 40% of patients with systemic lupus erythematosus (SLE). Such lesions can cause severe symptoms in coronary and brain circulations [2]. Stroke is the most serious complication, occurs in 20% to 30% of patients with autoimmune diseases, and is one of the main causes of death. There are ischaemic strokes, rarely occurring – haemorrhagic strokes, and so called silent (asymptomatic) strokes. Symptoms in silent stroke are non-specific, however the patient may present with psychiatric disorders, such as progressive cognitive impairment [1].

The neuropsychiatric symptoms are present in most autoimmune diseases. In some diseases, like SLE, they are included in diagnostic criteria and often prevail in clinical picture. In other diseases, like rheumatoid arthritis (RA) – they are rather associated with the awareness of a chronic disease inevitably leading to disability. In some autoimmune diseases (like systemic sclerosis or necrotizing vasculitis) neurological symptoms involving the peripheral nervous system are more common.

In this article neuropsychiatric problems in certain autoimmune diseases, the influence of immunosuppression on psychiatric symptoms and the role of psychiatric drugs on the induction of autoimmunization are discussed.

Rheumatoid arthritis

RA is the most common autoimmune, inflammatory disease of the joints. It affects 0.5%-1% of the general population and is 2-3-fold more common among women. The highest morbidity is observed in 4th and 5th decade of life [3]. RA mainly affects joints leading to permanent deformations and, as a consequence, handicap, progressive disability and early death. Patients present also with various extra-articular manifestations and systemic complications [4].

The neurological changes in RA are mainly associated with peripheral nervous system including symptoms induced by compression, inflammation and paresis of peripheral nerves. The main psychosocial factors, that negatively influence the adaptation to the chronic rheumatologic disease include depression and anxiety, exposure to stressors, and disturbance in sleep patterns. The frequency of depression and anxiety disorders among patients with RA ranges from 14 to 42% [5, 6]. Among female patients with RA who committed suicide, 90% had a depressive disorder [7]. The prevalence of these psychiatric disorders is substantially greater in patients with RA than in general population [8-10]. Patients with RA who experience depression report significantly higher levels of pain, greater number of painful joints, and poorer

functional ability [11, 12]. The presence of clinically significant comorbid depression is associated with an increased mortality rate [13]. Chronic rheumatologic disease may produce numerous stressors, including activity limitations and functional impairments at home and workplace, financial hardships produced by loss of income and high health costs, changes in physical appearance, and altered social relationships [14]. Liang et al. showed that approximately one-half of patients with RA reported dysfunction in social interactions, communication with others, and emotional behaviour [15]. It has been consistently noted that criticism from spouses is associated with poorer psychological adjustment among RA patients, whereas strong marital relationships tend to modulate the association between stress and increase in disease activity [16]. Increases in daily stressors lead to increased joint tenderness, global pain ratings, and altered immune system responses [16-18]. Abnormalities in the hypothalamic-pituitary-adrenal axis are involved in the association between stress and disease activity in patients with RA [19]. Exposure to stressors also may lead to cognitive distortions, such as "learned helplessness", characterized by emotional, motivational, and cognitive deficits in adaptive coping to stressful situations and strong belief that no viable solutions are available to eliminate or reduce the underlying source of stress [20]. Greater levels of helplessness predict greater flare activity in patients with RA [21]. Variety of different strategies of coping with a chronic disease are being instituted in RA, including education and learning skills of how to deal with a disease and prevent relapses [22].

In the last 20 years there has been a breakthrough in the RA treatment associated with the introduction of biological disease-modifying drugs and special therapeutic strategies that timely combine different medications to achieve remission. Such approach means increased treatment efficacy, better quality of life and decreased incidence of psychosocial problems in RA patients. Unfortunately, these new biological therapies are still very expensive and only few countries can afford to offer them for all needing RA patients [23].

Systemic lupus erythematosus

SLE is a prototypic systemic autoimmune disease with a broad spectrum of clinical presentations. Prevalence rates are estimated at 51 per 100 000 people in the USA. Women are affected nine times more frequently than men. SLE tends to be milder in elderly with lower incidence of malar rush, photosensitivity, purpura, alopecia, Raynaud's phenomenon, renal and CNS involvement, but greater prevalence of serositis, pulmonary involvement, sicca symptoms, and musculoskeletal manifestations [24]. Over the past 40 years, survival has improved significantly in patients with SLE. Approximately 90% of patients with SLE live more than 5 years. In early stages of SLE infections and disease activity are the leading death causes, whereas in a long-term course of the disease patients die due to the cardiovascular complications induced by early atherosclerosis [2].

SLE affects both CNS and peripheral nervous system (PNS), which can increase mortality. The American College of Rheumatology (ACR) described case definitions and classification criteria for 19 CNS and PNS syndromes observed in patients with

SLE, which are referred to as neuropsychiatric SLE (NPSLE) syndromes. The CNS syndromes include: aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache (including migraine and benign intracranial hypertension), movement disorder (chorea), myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, and psychosis. A psychiatric disturbance due to CNS lupus is a diagnosis of exclusion. All other possible causes of the observed symptoms should be considered, including infection, electrolyte abnormalities, renal failure, drug effects, mass lesions, arterial emboli, and primary psychiatric disorders (such as bipolar disorder) [25]. An important clue to the diagnosis is that most acute psychiatric episodes occur during the first two years after the diagnosis of SLE [26].

The term lupus cerebritis refers to the neuropsychiatric manifestations that appear to have an organic basis. Some authors underline a strong link between neuropsychiatric symptoms and the presence of some autoantibodies, including antineuronal antibodies [27, 28]. Some studies showed an association between antiribosomal P antibodies and psychosis and depression in SLE [29]. Other authors did not confirm this relation [28, 30]. It has also been suggested that there is a link between cognitive impairment and the presence of some specific autoantibodies in SLE [31-33]. No relation has been shown between antibodies against C1q (that might play a role in renal exacerbations) and neuropsychiatric manifestations in lupus [35].

A functional (psychological) process is assumed in a patient with cognitive impairment who has none of these antibodies, a negative magnetic resonance imaging (MRI) and electroencephalopathy (EEG), and psychometric testing that "rules out" organic disease. The prevalence of neuropsychiatric manifestations in SLE has the following order (from most to least prevalent): cognitive dysfunction, headache, mood disorder, cerebrovascular disease, seizures, polyneuropathy, anxiety disorder, and psychosis [36]. Organic psychosis occurs in approximately 3.5 – 5% patients with SLE, usually within the first year of diagnosis. Psychosis is characterized by bizarre thinking that often includes delusions and hallucinations. Some patients may also present with a fluctuating delirium or "clouding of consciousness", typically occurring at night. Other symptoms include a poor attention span, easy distraction, misinterpretation of surroundings, agitation, and aggressive behaviour. These symptoms may be caused by corticosteroid treatment or, more commonly, by CNS lupus. Auditory hallucinations are usually caused by steroid therapy, while visual and tactile disturbances are most frequently due to SLE. Psychosis due to organic involvement by SLE usually responds well to steroids. If no improvement is seen within 2-3 weeks, a trial of cytotoxic therapy (eg. cyclophosphamide pulse) is warranted [37]. Azathioprine is an effective and safe alternative for a long-term maintenance therapy [38]. While waiting for the effect of steroids and immunosuppressive therapy, psychiatric symptoms are best treated with typical antipsychotic drugs (such as haloperidol), as well as with active support by health caretakers and family members. Oral and intramuscular administration is preferred to intravenous because a significant prolongation of QT interval may occur more often with the latter route.

Cognitive dysfunction is an organic mental syndrome characterized by any combination of the following symptoms: difficulty of short or long-term memory, impair

judgment and abstract thinking, aphasia, apraxia, agnosia, and personality changes [39]. The incidence of cognitive defects range between 21 and 80% [31, 40]. There is a disagreement regarding the association between cognitive dysfunction and the antibodies implicated in other neuropsychiatric manifestations of CNS lupus. The association between antibodies to ribosomal protein P and cognitive impairment in SLE has not been confirmed [30]. Cognitive dysfunction is more common in patient with active SLE who are treated with corticosteroids [31]. There are two types of memory dysfunction in SLE: impaired remote memory is associated with a history of past CNS involvement, while impairment of immediate memory and concentration implies increased disease activity that may represent transient and diffuse CNS effect [41]. Associated conditions such as hypertension or multiple small infarcts may produce or potentiate cognitive dysfunction in SLE.

Treatment is based upon the suspected etiology of the cognitive abnormalities. If due to medications, such as steroids, reducing or stopping therapy should be considered. If associated with antiphospholipid antibodies, anticoagulation should be started. If associated with antineuronal antibodies, a short course of steroids (0.5 mg/kg for a few weeks) may be beneficial. Cognitive retraining using a combination of functional strategy training and psychosocial support may be effective in patients with persistent symptoms [42]. Regular use of aspirin may help prevent a decline in cognitive function, especially in elderly, and is strongly recommended in cardiovascular incidents prevention [43].

Dementia is a severe cognitive dysfunction, resulting in impaired memory, abstract thinking, and a decreased ability to perform simple everyday tasks. The patient may also have problems with decision making and controlling impulses. This syndrome in patients with SLE is usually associated with multiple small ischaemic strokes caused by antiphospholipid antibodies. Addition of antimalarial drugs, especially hydroxychlorochine, may have a protective effect. Dementia may be also due to vascular ischaemic lesions caused by early atherosclerosis in patients with SLE [2].

Secondary psychiatric manifestations, such as depression, anxiety and maniac behaviour are usually functional. The characteristic neuropsychiatric symptoms in SLE include: phobias, depression, anxiety, mania, paresthesias, headaches, mood swings, agoraphobia (with and without panic), social phobia, alcohol abuse, cognitive problems such as poor concentration, impaired memory, and difficulty with word finding or spatial orientation [31]. Interactions between the patient and physician may adversely affect symptom resolution. Patients are often frustrated by a long diagnostic process, and physicians may have difficulty dealing with patients with psychiatric problems [32]. Depression is the most common psychiatric symptom in patient with SLE. Depressive symptoms usually begin acutely and may reflect the patient's reaction to chronic illness and the significant lifestyle limitations, including difficulties with pregnancy, fatigue, limited sun exposure, chronic medication use and limited social support [44]. Following the initial diagnosis of SLE, or after an acute exacerbation, some patients present anxiety symptoms, either instead or in addition to depression. Patients become anxious about possible consequences of their illness, including disfigurement, disability, dependency, loss of a job, social isolation, or death. Anxiety may be manifested by

somatic symptoms. This state may deteriorate into obsessive-compulsive behaviour, phobias, hypochondrias, sleep disturbances, and a reduction in social contacts.

Rarely, patients develop maniac behaviour or an organic personality disorder. This behaviour is usually due to high doses of steroids. Patients present with emotional liability, sexual indiscretions, verbosity, religiosity, and/or aggressiveness [39].

Antiphospholipid syndrome

The neuropsychiatric symptoms in antiphospholipid syndrome (APS) are similar to those seen in SLE, because antiphospholipid antibodies are detected in up to 50% of patients with SLE. Whereas, so called primary APS, the most common acquired thrombophilia, is characterized by venous and arterial thrombosis (mainly in cerebral vascular bed), habitual abortions and other pregnancy complications with the coexistence of antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, and/or antibodies to beta2 glycoprotein I. The CNS symptoms include stroke, chorea, transverse myelitis and progressive dementia [1, 45]. The most common psychiatric symptom is cognitive impairment. It might be discrete or present as a severe dysfunction, such as generalized amnesia. Cognitive dysfunction in APS is usually associated with the presence of vascular lesions in white matter. It may coexist with characteristic skin lesions called "livedo reticularis". The vascular lesions in white matter observed in APS are difficult to differentiate in MRI from demyelination lesions seen in multiple sclerosis. Moreover, in some patients with multiple sclerosis, antiphospholipid antibodies might be detected [1].

Other autoimmune diseases

In other autoimmune diseases, neuropsychiatric symptoms are less common than in SLE and APS. In Sjögren's syndrome, also called sicca syndrome, the neuropsychiatric manifestations may mimic multiple sclerosis. Antiobodies SS-A (anti-Ro) are usually detected. The most common psychiatric symptoms include anxiety diagnosed in up to 48% of patients, and depression seen in approximately 32% of patients with Sjögren's syndrome [1].

Systemic sclerosis is a rare disease leading to fibrosis of the skin, subcutaneous tissue, and internal organs (lungs, kidneys, heart ant gastrointestinal tract) causing their failure. It is also characterized by the impaired morphology of blood vessels leading to Raynaud's phenomenon and primary arterial pulmonary hypertension, and immune system abnormalities [46]. Neuropsychiatric symptoms are rare and affect mainly peripheral nervous system. The most common psychiatric manifestation is depression due to chronic disease [1].

Systemic vasculitides

The vasculitides are a heterogeneous group of relatively rare conditions that can occur independently, like Wegener's granulomatosis, or as a secondary feature of an

established connective tissue disease. The symptomatology of systemic vasculitis is diverse and depends on the size of the vessels involved in the inflammatory process. The neurological symptoms result from the ischemia of the nervous tissue. Psychiatric symptoms are relatively common in Behçet's disease, characterized by vasculitis involving arteries and veins of large, medium and small sizes [1]. Approximately 20% of patients present with neurological symptoms, including aseptic encephalitis and meningitis, arteritis and venous sinus thrombosis. Some patients may have progressive personality changes, dementia, depression, and amentia [47].

In polyarteritis nodosa (PAN) approximately 70% of patients suffer from neurological symptoms, mainly peripheral neuropathy. The CNS symptoms might be secondary to arterial hypertension, diagnosed in most patients with PAN. Psychiatric manifestations are relatively common, including psychosis, especially in young patients, who are sometimes hospitalized in psychiatric units, before establishing the final diagnosis of PAN [1].

Peripheral nervous system is similarly involved in Churg-Strauss syndrome, a necrotic, granulomatous vasculitis, characterized by bronchial asthma and peripheral eosinophilia. Psychiatric manifestation, like psychosis and orientation disorders are quite rare [1].

Psychiatric complications of the treatment of autoimmune diseases

Systemic corticosteroids are used in the treatment of practically all autoimmune diseases. Unfortunately, with long use, especially higher doses of systemic corticosteroids, patients experience numerous side effect, including neuropsychiatric symptoms. Most psychiatric manifestations are mild and reversible after withdrawal or decreasing a dose of steroids. Most common psychiatric symptoms induced by steroid therapy include: emotional liability, hypomania, mania, depression, psychosis, delirium, confusion, or disorientation (especially in older patients), cognitive changes and memory deficits [48]. Sleep disturbances are reported, especially with split doses which may interfere with normal pattern of diurnal cortisol synthesis. Akathisia (motor restlessness) is a relatively common steroid therapy side effect. Older patients are at higher risk of steroid induced depression, mania, delirium, confusion, or disorientation [49]. At the beginning of corticoid therapy patients often experience agitation, a sense of wellbeing, euphoria, or hypomania, even prior to the improvement of the underlying disease. Depression usually develops later and with longstanding therapy [48, 49]. Patients with a family history of depression and alcoholism are at greater risk of affective diseases when treated with glucocorticoids. More severe psychiatric symptoms may develop very fast, within a few days, with higher doses of corticosteroids. Patients experience psychotic symptoms when treated with steroid doses higher than 20 mg of prednisone. Approximately 10% of these patients require not only the reduction of steroid dose, but also additional treatment with antipsychotic drugs. The response to such treatment is usually complete and occurs within two weeks of initiation of neuroleptics. Patients with SLE and hypoalbuminemia are at increased risk of steroid-induced psychosis. It is often difficult to differentiate between glucocorticoid-induced psychosis from

neuropsychiatric lupus in patient on high doses of steroids [49]. Patients treated with small to moderate steroid doses are at risk of partial memory loss and the risk is even greater in older patients [49]. About 1% of patients may be affected by more severe and persistent cognitive disturbances. One study showed a 5 to 7-fold increased risk of completed and attempted suicide among patients treated with glucocorticoids. Pseudotumor cerebri and panic disorder are rare side effects of steroid therapy [50].

Other immunosuppressive drugs used in autoimmune diseases therapy can induce psychiatric symptoms in rare cases. Finding a correlation between these symptoms and particular drug might be problematic, because majority of patients receive glucocorticoids at the same time. Therefore, it is difficult to demonstrate if the drug induced the psychiatric symptoms or just potentiated the side effects of steroids.

Antimalarial drugs (chloroquine and hydroxychloquine), that are widely used in the treatment of milder forms of SLE, RA and Sjögren's syndrome, may also induce psychiatric symptoms. Chloroquine is the only drug available in Poland, whereas in other countries hydroxychloroquine is being used much more frequently [51]. In SLE antimalarials are added to steroid therapy, whereas in RA they are used along with nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying drugs, such as methotrexate or sulfasalazine. The neuropsychiatric symptoms during a treatment with antimalarial drugs are usually mild and transient. Patients might experience headache and dizziness, other symptoms like emotional disturbances, agitation, insomnia, nightmares, anxiety, fatigue, delusions, hallucinations, and psychosis are extremely rare.

The role of psychiatric drugs in the autoimmunity induction

Numerous drugs induce the synthesis of autoantibodies, however in most cases a patient does not develop an autoimmune disease (drug-induced lupus in most cases). Drug-induced lupus should be suspected in patients with no diagnosis or history of SLE who develop antinuclear antibodies and at least one clinical symptom of lupus after an appropriate duration of drug exposure, and whose symptoms resolve after a discontinuation of the therapy. Most common clinical features of drug-induced lupus include: fever, myalgias, rash, arthritis, and serositis. Haematological abnormalities, kidney disease and CNS lupus are rare. Antihistone antibodies are present in 95% of cases, whereas hypocomplementaemia an anti-DNA antibodies are uncommon.

Some antipsychotic drugs may induce lupus-like disease, however the risk of this side effect is relatively low. Most frequently drug-induced lupus develops after treatment with chlorpromazine. Seldom cases are reported after perphenazine, phenelzine (the drug is not registered in Poland), and lithium carbonate [24]. In a case of drug-induced lupus, the suspected medication should be withdrawn. In some case patients may require the use of NSAIDs or antimalarial drugs, occasionally – glucocorticoid therapy [24].

Summary

The frequency of neuropsychiatric manifestations in autoimmune diseases depend on a type of a disease. These symptoms might reflect the reaction to severe chronic

disease or, like in SLE, be included in the diagnostic criteria of the disease. They are always a big diagnostic challenge and one of the main mortality causes in SLE. It is important to differentiate between functional and organic changes, primary and secondary to the treatment, vascular and immunological complications. Proper differential diagnosis has important therapeutic implications, because it helps adjust the intensity of anti-inflammatory and immunosuppressive treatment or make decisions concerning anticoagulation and atherosclerosis prevention. The most common psychiatric manifestation is a discrete cognitive impairment, that the patient is not aware of, and health care professional is not able to evaluate. Therefore, the cooperation with the patient's relatives in the diagnostic and therapeutic processes, is extremely important.

In patients treated with antipsychotic drugs, who develop autoantibodies and autoimmune symptoms, the diagnosis of drug-induced lupus should be considered and the change of treatment might be warranted. A close cooperation of an internist, an immunologist or rheumatologist with a psychiatry specialist is strongly advisable in dealing with patients with autoimmune diseases suffering from neuropsychiatric complications.

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