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Skin lesions – a valuable sign in the diagnosis of dementia syndromes

Zmiany skórne – cenna wskazówka w diagnostyce zespołów otępiennych

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S u m m a r y

Dementia syndromes are diseases of complex etiology and often a shared clinical picture. That causes great difficulties in the diagnosis. To deal with that, modern medicine is searching for methods to allow for a swift and explicit diagnostic method. In this respect, special attention is drawn to the characteristic skin lesions associated with certain types of dementia syndromes. The skin with its appendages (nails and hair) and the nerve tissue originate in the same germ layer: the ectoderm. That determines their inherent clinical association. Such co-existence of symptoms of the same foundation is present in Sneddon's syndrome and blue rubber bleb nevus syndrome (BRBNS). In Alzheimer's disease, lesions occur in the hair and nails, and the sympathetic sudo-secretory skin response is disturbed. Attention should be also drawn to disease syndromes, i.e. the CADASIL syndrome and Lafora disease, in which the skin biopsy forms the basis for diagnosis. Therefore, it seems that the skin manifestations associated with dementia syndromes can serve as a valuable sign in the course of diagnosis.

S t r e s z c z e n i e

Zespoły otępienne są schorzeniami o złożonej etiologii i często podobnym obrazie klinicznym. Powoduje to duże trudności diagnostyczne. Aby sobie z tym poradzić, współczesna medycyna poszukuje metod pozwalających na szybką i jednoznaczną diagnostykę. W tym aspekcie szczególną uwagę zwracają charakterystyczne zmiany skórne towarzyszące pewnym typom zespołów otępiennych. Skóra wraz z przydatkami (paznokciami i włosami) oraz tkanka nerwowa pochodzą z tego samego listka zarodkowego – ektodermy. Warunkuje to nieodłączne ich powiązanie kliniczne. Takie współwystępowanie objawów o tym samym podłożu obecne jest w zespole Sneddona oraz zespole gumiastych pęcherzyków znamionowych (ang. *blue rubber bleb nevus syndrome*). W chorobie Alzheimera obecne są zmiany we włosach i paznokciach oraz zaburzona jest reakcja potowo-wydzielnicza współczulna skóry. Uwagę zwracają także zespoły chorobowe, tj. zespół CADASIL i choroba Lafora, w których biopsja skóry stanowi podstawę rozpoznania. Wydaje się zatem, że manifestacje skórne towarzyszące zespołom otępiennym mogą być cenną wskazówką w ich diagnozowaniu.

INTRODUCTION

In today's world, dementia syndromes are a major problem for the humankind. They finally prevent the patients from living active social lives and cause their dependence, disability and alienation. Often, the only way to help those affected by the disease is to immediately diagnose it and start treatment, thus inhibiting/delaying its progression at the earliest possible stage.

DEMENTIA – THE DIVISION AND DEFINITION

According to the IGERO group's statement on dementia, based on the definition of the World Health Organization (ICD-10) and the American Psychiatric Association (DSM-IV), dementia is a syndrome caused by a brain disease of a chronic or progressive nature. The criteria for diagnosis of dementia include disorders of at least two cognitive functions always affecting the memory. The disorders are usually accompanied or

preceded by the patient's reduced control over emotions and behavior. Important criteria for the diagnosis of dementia syndrome include the patient's impaired independence, disorders of everyday life functions and persistent or progressive symptoms present for at least 6 months. The disease leads to a gradual withdrawal from social activity resulting in an increased dependence on the assistance and care provided by others (tab. 1) (1).

Age is an independent and crucial risk factor for dementia. That is confirmed by European statistics which show that while dementia syndrome occurs in 0.7% of people aged 62, it affects 20-50% of patients over the age of 85; however, in centenarians the proportion relates to as much as 60% (2).

Table 1. The most common causes of dementia.

No.	Causes of dementia
1.	Degenerative changes
2.	Vascular lesions
3.	Infectious agents
4.	Toxic agents
5.	Metabolic disorders
6.	Injuries to the central nervous system

In addition to specific skin symptoms, such as the changes in the structure of hair and nails in Alzheimer's disease or the skin lesions associated with dementia of vascular origins, also nonspecific changes occur in progressive dementia. Dementia is often accompanied by skin lesions resulting from neglected hygiene, i.e. bedsores, excoriation, mycoses, bacterial infections, posttraumatic wounds (due to disturbance of gait, imbalance or clumsy movement) and itching. We should not forget about iatrogenic lesions resulting from the use of applied forms of therapy (the most common are: itchy skin, cutaneous discoloration, allergic reactions).

Considering dermatological aspects in various types of dementia syndromes, the following can be distinguished: skin lesions resulting from neglected hygiene, itching, iatrogenic lesions, skin lesions that are a part of syndromes with coexisting dementia, dementia-associated lesions of vascular origins, hair and nail disorders in Alzheimer's disease, skin as the location of diagnostic indicators of dementia (3).

SKIN LESIONS IN DEMENTIA OF VASCULAR ORIGINS

In those patients who suffer from dementia associated with vascular lesions, cutaneous manifestations are often observed in the form of *livedo reticularis* (reticular cyanosis), which is an important diagnostic criterion. In Sneddon's syndrome – an autoimmune disease of unknown etiology – dominant symptoms are associated with a temporary closure of blood vessels within the central nervous system in the form of ischemic strokes, related progressive dementia and visual damage. Simultaneously, skin lesions accompany reticular

cyanosis lesions. Often, also the kidneys and heart are affected. A different etiology and the absence of anticardiolipin antibodies allow us to differentiate the disease from the anticardiolipin syndrome (4, 5).

That group also includes the rare blue rubber bleb nevus syndrome (BRBNS). It occurs rarely, with a probable autosomal dominant inheritance. Its picture is composed of the characteristic painful, tender and multiple cavernous angiomas. These can be located in various skin areas, but mostly on the face and limbs. Similar vascular lesions also appear within the gastrointestinal tract and in the central nervous system, where – through extravasations and vascular malformations – they can lead to ischemia and, as a consequence, to dementia (6).

HAIR AND NAIL LESIONS IN ALZHEIMER'S DISEASE

In that disease the specific lesions within the hair and nails and the changes occurring in the sympathetic sudo-secretory response are dominant.

Special attention is drawn to the lesions generated within the nails. Studies show a correlation between a reduction in the concentration of mercury and the duration and severity of dementia. Changes in the concentration of micronutrients in the nail plate (calcium, magnesium, mercury, potassium, zinc, bromine, cobalt) are observed at the earliest stages of the disease. A negative correlation between the concentration of aluminum and blood flow in the brain has also been shown (7, 8). Studies of human hair show that in 85% of patients diagnosed with Alzheimer's disease the hair structure is abnormal. In comparison, that parameter would account for 35% in the control group. Pseudo-curly hair is dominant (*pseudopili torti*) – 70%; split hair (*trichorrhexis nodosa*) (7).

Assessment of the autonomic sudo-secretory function is a neurophysiological test used to assess the functioning of the sympathetic nervous system. Sympathetic skin response is a reflex reaction of the sudo-secretory system. It is produced in response to endogenous stimuli, such as deep breath, or exogenous stimuli, such as current stimulation in the form of the polysynaptic reflex arc, whose afferent arm is made of the rapidly conductive myelin fibers and whose efferent arm is made of the postganglionic sympathetic fibers. In this study sympathetic skin response was induced by placing plate-shaped receiver electrodes on the patient's left palm and foot and stimulating the corresponding nerve bundles with electrical current. Under physiological conditions, by stimulating the reflex arc, the stimuli are summated in the vegetative structures of the central nervous system, whereby sweat glands of the skin are stimulated synchronously, which is accompanied by a voltage change on the skin. A pathological response is a disorder of the central or peripheral conduction. The study examined the sympathetic sudo-secretory response; it covered 21 subjects (12 men and 9 women) diagnosed with Alzheimer's disease; the control group consisted of 22 healthy individuals.

The value of an average patient's latency was recorded in the foot and palm; it was significantly longer than the one in the control group; in 3 cases of palms and 4 cases of feet, sympathetic skin response was not recorded. Researchers suggest that changes occurring most frequently in the form of extended latency are most likely due to a disturbance in the central part of the reflex arc (as in some multifocal diseases of the central nervous system) (9).

THE PERIPHERAL BIOMARKERS OF ALZHEIMER'S DISEASE

The necessary condition for the diagnosis of Alzheimer's disease is the occurrence of dementia. However, it is known that pathological abnormalities (amyloid plaques and neurofibrillary tangles) occur about 10-20 years before the symptoms of cognitive disorders and severe loss of neurons. Early diagnosis in patients with no cognitive impairment, before the loss of neurons and synapses, and the use of new future therapies, give us hope to maintain the normal function of the brain (10).

A biomarker was defined by Hulk as "a cellular biochemical or molecular change that is clearly marked in biological environments, such as human tissues, cells or body fluids" (11). The ideal biomarker for Alzheimer's disease should reflect the basic neuropathological and neurophysiological characteristics. The establishment of a biomarker should be reliable and reproducible, non-invasive, simple to perform and inexpensive. An optimal biomarker should be detected in a diagnostic attempt which is fast, easy, safe, acceptable for the patient and physician, and most importantly – it must allow us to reveal the disease in the preclinical phase (12). The basic modern biomarkers reveal the brain pathology which underlies the disease. These biomarkers include: β-amyloid, tau protein and protein candidates for biomarkers – BACE1, ubiquitin, neurofilament protein (NF), neuromodulin (GAP43), NTP and AD7c proteins; the less specific markers: of inflammation (cytokines) and of oxidative stress (vitamin E, isoprostanes); and metabolic markers (24S-hydroxycholesterol) and sulfatides (phosphatidylinositol) (10). The use of biomarkers gives hope for an early and correct diagnosis of Alzheimer's disease but their actual usefulness needs to be confirmed in further studies. The best-known markers (e.g. β-amyloid, tau protein) are detected in the cerebrospinal fluid, which significantly limits their application. Currently, research is being conducted to establish whether disease biomarkers are present in peripheral tissues outside the central nervous system. β-amyloid and tau protein are also found in peripheral tissues, i.e. the skin. As compared to healthy individuals, the secretion of β-amyloid is increased by dermal fibroblasts in patients with Alzheimer's disease (13). Other irregularities in skin fibroblasts of the patients with Alzheimer's dementia have also been described. These include: disorders of DNA repair, abnormalities in the regulation of calcium ion levels, damage to the isozyme of protein kinase C, abnormal expression of genes in familial Alzheimer's disease, abnormalities of MAP kinase signaling pathways, p53 disorders, modified cholesterol metabolism, differences in the composition of the extracellular matrix (ECM) and abnormal binding of the folic acid in skin fibroblasts (14). An advantage of the biomarkers made from fibroblasts is the fact that they are collected from single skin specimens. It is a relatively inexpensive method, and it is non-invasive. A disadvantage may be that it is time-consuming; it takes approx. 4 weeks to obtain the results after the biopsy is collected, which is related to the fact that fibroblasts grow slowly. Currently, research is conducted to find a biomarker to enable the diagnosis of Alzheimer's disease at its preclinical stage.

SYNDROMES OF DEMENTIA – SKIN BIOPSY – DIAGNOSIS

Lafora progressive myoclonus epilepsy is a genetically determined form of epilepsy caused by mutations in the *EPM2A* gene, which encodes laforin, or the *NHLRC1* gene, which encodes malin. It starts in the second decade of life, when epileptic seizures, clonic convulsions of the muscles and progressive dementia are dominant. In such case, skin biopsy allows for an explicit diagnosis. The intracytoplasmic structures called Lafory cells are seen in the distal part of the efferent ducts of the eccrine glands in PAS staining (15).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is another disease accompanying dementia, whose diagnosis is based on skin biopsy. Recurrent episodes of subcortical strokes and ischemic attacks are present in the picture of that disease; these episodes lead to the formation of ischemic lesions within the basal ganglia and the white matter. The disease is associated with autosomal dominant inheritance – it is connected with a mutation in the *NOTH3* gene and it affects young people. The disease is manifested by paresis of the limbs and facial muscles and by disturbance of consciousness. Dementia develops gradually and in association with transient ischemic attacks (micro-strokes). Skin biopsy is a very specific examination. Grainy, dense material is revealed under electron microscopy within the cutaneous vascular wall (at the lamina basalis of the muscle cells) (16-18).

CONCLUSIONS

Along with the advancement of medicine, the number of elderly people has been constantly increasing. Due to the growing number of cases of dementia syndromes, it becomes necessary to diagnose them as fast and as accurately as possible. Coexistence of skin lesions perceptible at an early stage appears to be significant in the diagnosis of those diseases. Also, we should be aware that many dermatological aspects coexist with the underlying disease, i.e. itching, iatrogenic lesions and skin lesions resulting from neglected hygiene.

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