NEUROLOGICAL APPROACH TO DIABETES MELLITUS

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Abstract: *Diabetes mellitus is a global public health issue impairing the quality of the patient's life and it is also the most frequent cause of neuropathy. The diagnostic approach begins with the consolidation of the results obtained from the anamnesis, the patient's medical history and his/her neurological examination. Hyperglycemia poorly managed throughout the years leads to numerous complications, especially vascular (microvascular, macrovascular) ones. We are describing here the case of a 53-year old female patient, with significant cardiac pathology (high blood pressure, permanent atrial fibrillation), who has been suffering from obesity and diabetes mellitus for approximately ten years, under treatment with oral antidiabetics, in whom we see the sudden installation of a state of postural instability and language impairments. In the brain CT scan, an ischemic stroke is shown in the vertebrobasilar area. Apart from the neurological pathology, which includes motor disorders in the right hemibody with ataxia, mainly expressive aphasia, diplopia, the patient has also developed in time, at approximately 18 years after the installation of diabetes mellitus, a sensory-motor polyneuropathy, with edemas in the lower parts, blisters and superficial ulcerations in the right leg. Diabetic neuropathy occurs following the nervous ischemia in the microvascular disease and it can be seen in several forms: symmetric polyneuropathy, autonomic neuropathy, mononeuropathies, cranial neuropathies and radiculopathies. Chronic diabetes complications generate the increase of the morbidity and mortality rates – diabetes mellitus is one of the main risk factors of stroke.*

INTRODUCTION

Diabetes mellitus is the decrease of insulin secretion, as well as variable degrees of insulin resistance leading to hyperglycemia.(1)

Years of poorly controlled hyperglycemia lead to multiple complications, mainly vascular ones, acting on the small (microvascular) and/or large (macrovascular) blood vessels. The mechanisms by which the vascular disease appears are given by the glycation of serum and tissue proteins, with the formation of glycation end-products; superoxide production; activation of protein kinase C, a signal molecule increasing the vascular permeability and leading to endothelial dysfunction; the accelerated hexosamine biosynthesis and polyol pathways, which lead to the accumulation of sorbitol in the tissues; high blood pressure and dyslipidemia usually associated with diabetes mellitus; arterial micro-thromboses and the pro-inflammatory and pro-thrombotic effects of hyperglycemia and of hyperinsulinism, which have an impact on vascular self-regulation. Immunity dysfunction is another major complication and it occurs because of the direct effects of hyperglycemia on cell immunity.(1)

The microvascular disease is the basis of three of the best known and most severe manifestations of diabetes mellitus: retinopathy, nephropathy and neuropathy. Small vessel disease also has a dramatic impact on skin healing; thus, even the smallest injuries may evolve to deep ulcers and become easily infected. The intensive control of plasmatic glucose may prevent many of these complications, but it may not health them, once they are installed.(1)

Macrovascular disease – large vessel atherosclerosis is the result of hyperinsulinemia, dyslipidemia and hyperglycemia specific to diabetes mellitus. The symptoms are angina and myocardial infarction, transient ischemic attacks and peripheral artery disease.(1)

Hyperglycemia is a common issue and an important aspect in terms of acute stroke therapy and prognosis. Approximately 40% of the stroke-affected patients suffer from hyperglycemia upon their admission in the hospital; hyperglycemia means serum glucose levels higher than 120 mg/dl (higher than 7.0 mmol/l). Reactive hyperglycemia is more frequent in the people known with diabetes, but also in those with newly discovered (previously unknown) diabetic disease or as stress hyperglycemia, in people with normal blood sugar levels. Most of the patients, however, have transient stress hyperglycemia generated by an increased secretion of cortisol and norepinephrine. Hyperglycemia control in acute stroke cases is an important component in the prompt management of stroke.(2)

Experimental and clinical data have shown the detrimental role of hyperglycemia in acute stroke cases. Hyperglycemia worsens the experimental ischemic lesion, while the control of blood sugar levels reduces the injury. In the clinical assessment, hyperglycemia would be correlated with the initial volume of the infarction and would lead to the progression of the infarction in the neighbouring area with a moderate perfusion deficit. Pathogenically speaking, hyperglycemia increase the cerebral injury by the increase of acidosis (lactic acid, consequence of anaerobiotic metabolism),

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the generation of free radicals and the increase of hemato-encephalic permeability. In conditions of stroke thrombolysis, hyperglycemia reduces the benefits of recanalization and it associates with a hemorrhagic risk.(2)

The (fast acting) insulin treatment of hyperglycemia is a necessary measure, since persistent hyperglycemia in the first 24 hours is linked with an unfavourable evolution of acute stroke.(2)

CLINICAL CASE

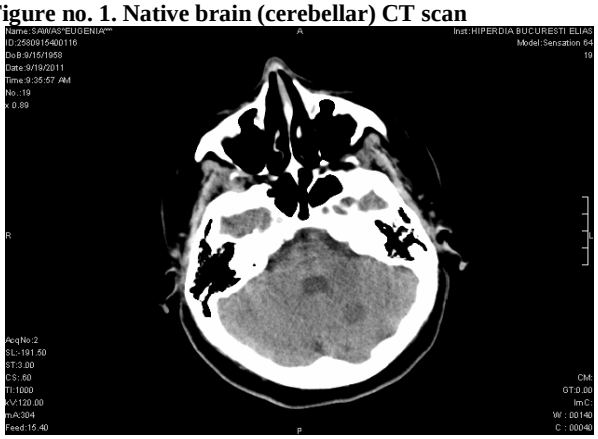
We are describing here the case of a 53-year old female patient, with significant cardiac pathology (high blood pressure, permanent atrial fibrillation), who has been suffering from obesity and diabetes mellitus for approximately ten years, under treatment with oral antidiabetics, in whom we see the sudden installation of a state of postural instability and language impairments. In the brain CT scan, an ischemic stroke is shown in the vertebrobasilar area. Apart from the neurological pathology, which includes motor disorders in the right hemibody with ataxia, mainly expressive aphasia, diplopia, the patient has also developed in time, at approximately 18 years after the installation of diabetes mellitus, a sensory-motor polyneuropathy, with edemas in the lower parts, blisters and superficial ulcerations in the right leg.

The neurological examination shows:

- conscious female patient, with a mild, especially expressive speech disorder;
- mild motor deficit in the right hemi-body and ataxia, especially of the upper limb, as sequelae;
- mainly distal bilateral weakening of muscle strength in the lower limbs;
- distal bilateral lower limb hypoesthesia;
- paresthesia;
- abolished bilateral Achilles deep tendon reflexes;
- declivitous edemas and superficial ulcerations in the right leg.

The known personal medical history (type II diabetes mellitus, ischemic heart disease, grade 3 arterial hypertension, permanent atrial fibrillation, class 3 obesity, ischemic stroke sequelae, rheumatic mitral stenosis) is completed by microvascular complications-sensory-motor polyneuropathy and leg ulcerations.

Figure no. 1. Native brain (cerebellar) CT scan



DISCUSSIONS

Approaching the patient who suffers from peripheral neuropathy.

When dealing with this group of diseases, the clinician is first confronted with a number of issues to be solved sequentially:

1. he/she needs to establish the presence of the peripheral nervous system disease and to differentiate from a process of the central nervous system, neuromuscular junction or muscles;
2. with the clinical examination, he/she needs to find which of the main topographic syndromes are present;
3. by examination and nerve conduction studies, he/she needs to see whether the issue of mainly motor, sensory or vegetative or whether it is mixed and whether the myelin sheath, the axon or the cell body (motor or sensory neurons) is the target of the disease;
4. to assess whether the neuropathy is acquired or hereditary.(3)

Taken together, these characteristics enable the limitation of the probable etiologic diagnoses from a wide list of possibilities.(3)

What are the most common diseases affecting the peripheral nerve?

- Alcohol
- Amyloid
- Diabetes
- Environmental toxins and drugs
- Guillan-Barre
- Hereditary
- Infections
- Nutritional
- Paraneoplastic
- Rheumatic(collagen vascular)
- Systemic disease
- Trauma
- Tumours (4)

What is the anatomy of a peripheral nerve?

The outer layer of a peripheral nerve is called the epineurium. Each nerve is made up of a bundle of nerve fibers called fascicles and each fascicle is surrounded by a perineurium. Each fascicle is made up of a number of axons and each axon is sheathed in the endoneurium.(4)

What are the electrophysiologic mechanisms that correlate with weakness in peripheral neuropathy?

Conduction block, denervation with loss of motor units, and failure of neuromuscular transmission. One or more of the above are needed. Slowing of motor conduction velocity in itself, even if severe, does not result in weakness.(4)

What is the most common cause of peripheral neuropathy in the world?

Diabetes mellitus. Approximately 150 million people have diabetes and up to half of them have symptomatic diabetic neuropathy. The prevalence of diabetes is increasing every year. Alcoholic neuropathy is the second most common cause of peripheral neuropathy. Therefore, all patients with distal symmetric polyneuropathy should be screened for diabetes mellitus as well as unhealthy alcohol use. Leprosy was once the most common cause of neuropathy worldwide, but its incidence has dramatically decreased since 1982.(4)

What are the clinical forms of diabetic neuropathy?

Diabetic neuropathies include distal symmetric sensory or sensorimotor polyneuropathy, small fiber neuropathy, diabetic neuropathic cachexia, hypoglycemic neuropathy, treatment – induced neuropathy (insulin neuritis), polyradiculopathy, diabetic lumbosacral radiculoplexus neuropathy (diabetic amyotrophy)/ mononeuropathies, and cranial neuropathies.(4)

Distal symmetric sensory polyneuropathy, the most common form, is a slowly progressive length-dependent axonal sensory polyneuropathy that presents with numbness and

paresthesias in the feet, usually minimal motor weakness, and possibly autonomic changes.(4)

What are the risk factors for developing diabetic peripheral neuropathy?

- Duration of diabetes
- Degree of glycemic control
- Older age
- Male sex
- Excessive alcohol consumption
- Nicotine use
- Dyslipidemia
- Angiotensin-converting enzyme D allele (4)

Diabetic neuropathy is the most common microvascular complication of diabetes, and it is a major cause of morbidity and mortality. Diabetic neuropathies comprise a heterogeneous group of conditions that affects different parts of the nervous system and presents with diverse clinical manifestations. The early recognition and appropriate treatment of diabetic neuropathy is essential because:

- it represents a diagnosis of exclusion;
- different therapies are available for the symptomatic forms;
- up to 50% of the peripheral neuropathies may be asymptomatic.(5)

Distal symmetric polyneuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.(5)

The diagnosis of distal symmetric polyneuropathy is mainly clinical and „the combination of typical symptomatology and symmetrical distal sensory loss or typical signs in the absence of symptoms in a patient with diabetes„ highly suggests its presence.(5)

The need to facilitate the diagnosis in clinical practice led to the development of clinical scores. The Michigan Neuropathy Screening Instrument (MNSI), the modified Toronto Clinical Neuropathy Scale (mTCNS), the Utah Early Neuropathy Scale (UENS) and the Neuropathy Disability Score (NDS) are currently recommended by the ADA (American Diabetes Association) with or without corneal confocal microscopy and intraepidermal nerve fiber density in distal symmetric polyneuropathy.(5)

The form of distal, symmetrical, mainly sensory polyneuropathy is the most common type. Usually, it is a chronic process, sometimes unnoticed by the patient. The main complaints are given by persistent and sometimes bothersome paresthesia and tingling, generally limited to the foot and the lower leg, more irritating at night. Achilles reflexes are absent and so are, at times, the patellar reflexes. As a rule, the abolition of sensitivity is limited to the distal parts of the lower extremities, but the severe cases also involve the hands and the sensory impairment may also extend to the anterior trunk, simulating a sensory level similar to a spinal cord disorder. Trophic changes, in the form of deep ulceration and the neuropathic degeneration of the joints (Charcot joints) can be seen in the most severe and long-lasting cases, possibly as a result of the sensory analgesia, of the trophic changes and of the repetitive injuries (plantar ulcerations are simply more frequent because of the microvascular disease of the integument at the people suffering from diabetes.(3)

The pathogenic basis for distal symmetric polyneuropathy is unknown and controversial. The major theories involve a metabolic process, ischemic damage, or an immunologic disorder. The neuropathy is slowly progressive but can stabilize or improve with tight control of diabetes.(6)

CONCLUSIONS

Diabetes mellitus is a public health issue; its complications increase the morbidity and mortality rates.

Diabetes mellitus is more than a chronic disease where the treatment should be customized; it is a physical, psychological and emotional impairment.

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