THERAPEUTIC PERSPECTIVES IN SNEDDON'S SYNDROME

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Abstract

Sneddon's syndrome is a rare but severe progressive chronic disease, characterized by multiple discoloration skin patches called Livedo racemosa and recurrent cerebrovascular events. It mainly affects women aged around 40. Considering the two main forms, antiphospholipid (APS) positive and negative, the available treatments are directed at either one of them. The idiopathic form (APS negative) is associated with a more severe prognosis as chronic oral anticoagulant therapy (COA) is more difficult to manage. One therapeutic perspective in controlling disease progression in these patients is by understanding the protein Z deficiency in these patients as a deciding factor in the success of the COA therapy.

Keywords: Sneddon's syndrome, chronic oral anticoagulation, protein Z deficiency.

Rezumat

Sindromul Sneddon este o afecțiune cronică progresivă rară, dar severă, caracterizată prin patch-uri multiple de decolorare a pielii numite Livedo racemosa și evenimente cerebrovasculare recurente. Afectează în principal femeile cu vârsta de aproximativ 40 de ani. Având în vedere cele două forme principale, antifosfolipidice (APS) pozitive și negative, tratamentele disponibile se adresează oricăreia dintre ele. Forma idiopatică (APS negativă) este asociată cu un prognostic mai sever, deoarece terapia anticoagulantă orală cronică (COA) este mai dificil de gestionat. O perspectivă terapeutică în controlul progresiei bolii la acești pacienți este înțelegerea deficitului de proteină Z ca factor decisiv în succesul terapiei cu COA.

Keywords: sindrom Sneddon, anticoagulare orală cronică, deficit de proteină Z.

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Introduction

Sneddon's syndrome is a chronic progressive disorder encountered most often in women, with the average age being 40 years old. It is a rare condition, being diagnosed in 4 cases/1.000.000 people/ year. Its main characteristics are the patches of discoloration on the skin (generalized livedo racemosa) and the recurrent cerebrovascular events. Based on the ethio-pathogenic profile, Sneddon's syndrome can be classified into two major forms: autoimmune/inflammatory (antiphospholipid (APL) positive) and idiopathic (antiphospholipid (APL) negative/thrombophilia).

The skin lesions can precede the cerebrovascular events by more than 10 years. Regarding the evolution of the neurological manifestations from prodromal symptoms to recurrent strokes and, finally, early onset dementia, one can see why the neuropsychiatric prognosis is poor, with the persistence of concentration and attention deficits.

Apart from those mentioned above, valvulopathies and labile systolic hypertension also suggest the cardiovascular involvement of the disease^(1,2,3,4).

While the genetic mechanisms are not yet fully understood, it is nevertheless suggested that of particular importance is the mutation in the cat eye syndrome region, candidate 1

(CECR1), encoding Adenosine deaminase 2 (ADA2)^(1,5).

Recently, it has been noted that most of the affected patients had a minimum of 3 cardiovascular risk factors and the median period between the first event and the diagnosis establishment is 2 years. However, as far as APL positive or negative forms go, no significant differences have been observed at the moment⁽⁶⁾.

Being a rare disease, with a long-term period between events and heterogeneous clinical manifestations, it is often under-diagnosed, being more a diagnosis of exclusion and the skin biopsy may be the only available means for an early identification⁽⁷⁾.

Brain imaging can also be useful as there are some radiological features of Sneddon's syndrome, such as cortical-subcortical supratentorial and cerebellar non-territorial infarcts, together with multifocal cerebral atrophy^(8,9).

Case presentation

We are presenting the case of a 49-year-old female patient, with known cardiovascular risk factors and pathologies (3rd degree primary hypertension, anterior mitral valve prolapse, moderate mitral valve regurgitation, chronic oral anticoagulation) and neurological (recurrent ischemic strokes, left spastic hemiplegia, vascular epilepsy), who is

Figure 1. Livedo racemosa spots on the abdomen

Figure 2. Livedo racemosa on both lower limbs

Figure 3. Left-sided spastic hemiparesis (left upper limb in a flexed position and the left lower limb extended)

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admitted in the Cardiology Clinic of the Clinical Rehabilitation Hospital of Iasi for labile blood pressure (BP) values at home, fast irregular palpitations and pressure-like anterior thoracic pain, radiating into the left upper limb, with a duration of 30 minutes and a spontaneous cessation. Regarding her family history, her mother suffered from a cutaneous disease (most likely Livedo Racemosa) and one brother and two aunts had ischemic strokes. The patient had 4 spontaneous miscarriages. At the moment she is retired, having previously worked as a housekeeper. She denies chronic smoking and alcohol consumption.

At the age of 20 the Livedo racemosa skin lesions first appeared and, 10 years later, at the age of 35, she suffers her first major ischemic stroke, accompanied by a left-sided spastic hemiplegia and vascular epilepsy. Five years later, at the age of 40, she suffers a recurrent major ischemic stroke.

Given the context of the associated pathologies - multiple strokes, 4 spontaneous miscarriages, remitted left-sided brachio-facial motor deficit, Livedo racemosa, hypertension - and the result of the Musculo-cutaneous biopsy (perivascular inflammatory infiltrate with bosellate endothelium), the diagnosis of Sneddon's syndrome was established. It was described as an idiopathic form (antiphospholipid negative) since the anticardiolipin antibodies (ACL), both IgG and

IgM, were within normal ranges. Further known pathologies include, at the age of 45, 3rd degree hypertension with a very high additional risk (maximum known systolic BP value of 180 mmHg), anterior mitral valve prolapse and moderate-severe mitral regurgitation.

In June 2020, the patient suffers a seizure paroxysmal attack during the night, with loss of consciousness, severe headache and sphincter relaxation. She admits to having suspended for a month prior her anti-convulsive medication and having consumed a higher than usual amount of coffee (a neuroexciter). She is admitted in the Emergency Department of the Neurosurgery Hospital where she undergoes a cerebral computed tomography (CT) examination. The result shows sequela cortical hypodense areas with localized ischemic appearance and cerebral lacunarism and the diagnosis of tonic-clonic epileptic seizures is established.

Upon admission, her treatment schedule was comprised of: Nebivolol 5 mg qd, Lisinopril 5 mg qd, Apixaban 5 mg bid, Carbamazepine 200 mg bid, Nicergoline 30 mg bid, Baclofen 26 mg bid.

During the physical examination, upon inspection, a central facial paresis was noted, along with livedo racemosa on both thighs, abdomen and back. She showed a left-sided spastic hemiparesis, with the left upper limb in a flexed position and the left lower limb

extended, and, during walking, a spastic gait. Regarding the cardiovascular system, on auscultation, a systolic murmur was heard in the left fifth intercostal (ic) space on the medial clavicular line, radiating onto the left carotid artery, while a weaker pulse wave was perceived in the periphery.

Given the patient's medical history, a neurological examination was deemed necessary, which concluded the following:

- Left-sided spastic gait, possibly without support at very short distances;
- Left lower limb motor deficit;
- MRC scale: distal lower limb 2/5, proximal lower limb 4/5, left elastic hypotonus.
- Right-sided Noica sign present;
- Left-sided Chadock sign present;
- Active Deep tendon reflexes more on the left side than on the right;
- Cranial nerves: old bilateral hyposmia (septal deviation), amblyopia (optical correction for reading), paresthesias and superficial hypoaesthesia on the left hemifacies, left-sided dynamic facial paresis, vertigo.
- Positive Romberg sign;
- Positive left-sided Babinski sign;
- Intermittent dysphagia for solid and liquid foods;
- Sensitivity in the left limb: paresthesias, superficial hypoaesthesia, deep anesthesia.
- Amnesic disorders;
- Particular attitudes: upper left limb in flexion, lower left limb in extension.

The laboratory test revealed elevated gamma-glutamyl transferase (GGT) values (160,1 UI/L), as well as for the C-reactive protein (1,22 mg/dl).

The at-rest electrocardiogram (ECG) showed

sinus rhythm, 75/min heart rate (HR), 21 degree QRS-axis, fragmented QRS complex in the D3 lead, negative T waves in the D3 lead and flattened T waves in the aVF lead.

The subsequent Holter-ECG investigation concluded a sinus rhythm for the whole duration of the recording, with an average heart rate of 76/min, ranging between 57-121/min, 12 isolated polymorphous ventricular premature beats, 50 monomorphous isolates supraventricular beats, with an S-V run of 3 beats, without any asystolic periods longer than 2,5 seconds and without any ventricular arrhythmias.

The heart ultrasound reports anterior mitral valve prolapse, 2nd degree mitral valve regurgitation, Hyperechogenic aortic walls - suggestive of aortic atheromatosis, moderate concentric left ventricular hypertrophy (LVH), delayed relaxation type diastolic dysfunction and a preserved left ventricular ejection fraction (LVEF).

Given the following established diagnoses:

1. 3rd degree essential hypertension with very high additional risk;
2. Mitral valve prolapse;
3. Moderate mitral regurgitation;
4. Chronic oral anticoagulation;
5. Recurrent strokes;
6. Left spastic hemiplegia;
7. Vascular epilepsy;
8. Sneddon syndrome;
9. Livedo racemose;
10. Previous cholecystectomy;
11. Left gonarthrosis;
12. Fibrocystic mastosis.

The following recommendations were made:

- Low-fat, low-lipid, low-calorie diet with the avoidance of animal fats;
- Avoidance of neuroexcitants (coffee, chocolate, black tea, green tea);

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- Adequate daily hydration - 2L fluids / day;
- Gradual weight loss;
- Avoidance of extreme temperatures and psycho-emotional stress;
- BP and HR monitoring at home;
- Avoidance of intramuscular (im) and subcutaneous (sc) injections, being allowed only the intravenous (iv) ones;
- Periodic cardiological and neurological evaluations;
- Dosage of GGT and renal parameters in one month.
- The treatment regimen included:
 - Nebivolol 5 mg qd;
 - Perindopril 5 mg qd;
 - Apixaban 5 mg bid;
 - Carbamazepine 200 mg bid;
 - Nicergoline 30 mg bid;
 - Baclofen 26 mg bid;
 - Lagosa 150 mg bid;
 - Stresclin Neuro bid.

This treatment aims at controlling the cardiovascular symptoms and risk factors (angina pectoris, essential hypertension) in order to slow the progression of the disease, avoid the occurrence of another cerebral ischemic event and limit the aggravation of the neuro-motor disability.

Chronic oral anticoagulation (COA) therapy prevents cerebral thrombotic events, and the

benefit must be balanced by the associated bleeding risk. The absence of APS is associated with poor control of the anticoagulant therapy, being an element of severe prognosis of the disease towards neurocognitive decline. Patient compliance with drug treatment and cardiovascular and neuromotor recovery is paramount to delay disease progression.

Discussions

It has been noted that in Sneddon's syndrome patients, there is a significant deficit of protein Z (a vitamin K-dependent coagulation inhibitor), which accounts for the increased incidence of thromboembolic events in these patients and underlines the necessity for antiplatelet/anticoagulant therapy⁽¹⁰⁾.

Antiplatelet therapy is a less aggressive alternative in patients with idiopathic Sneddon syndrome; it is, however, less effective in the presence of APS. While not significantly less effective than anticoagulant therapy, antiplatelet therapy may slow cognitive decline in Sneddon's syndrome patients and thus delay or even inhibit the onset of dementia⁽¹¹⁾.

Regarding anticoagulation therapy, the two main options are the antithrombotic K anticoagulants (AVK) and the new oral anticoagulants (NOAC). AVK therapy may be associated with a higher risk of bleeding,

especially in epileptic patients, in the context of frequent falls from the same level associated with possible intracranial hemorrhage.

Recent data show that the benefit of anticoagulant therapy at maximum dose targeting an international normalized ratio (INR) >3 in the absence of AFL is negligible. NOAC therapy is associated with a significant reduction in the frequency of intracranial hemorrhage episodes and significantly lower rates of stroke, mortality and hospitalizations and is useful in patients with moyamoya phenomena (neoformation vessels with increased fragility) secondary to chronic hypoxemia from diffuse vasculopathy⁽¹¹⁾.

An important differential diagnosis can be made with another rare and recently described disease, the lymphocytic thrombophilic arteritis, which also manifest with livedo racemosa. As Sneddon's syndrome is the more severe entity, differentiation between the two is critical, especially in the early stages.

Therefore, the histopathological findings are the ones that can help establish the correct diagnosis. While the lymphocytic thrombophilic arteritis is characterized by a dense lymphocytic inflammatory infiltrate affecting small to medium-sized arteries, Sneddon's syndrome shows proliferation of smooth muscle cells of the intima of the vessels, with their subsequent narrowing or occlusion⁽¹²⁾.

Conclusions

Optimal therapeutic management in patients with idiopathic Sneddon Syndrome remains unclear. Subsequent therapeutic perspectives should consider the discovery of a new common marker in both idiopathic Sneddon Syndrome and APS-associated Sneddon Syndrome.

However, the biological status of APS is not the only important criterion in stratifying the thromboembolic risk and in guiding the antithrombotic therapy in accordance with the pathogenesis of the disease. The status of the Z protein in patients with idiopathic Sneddon Syndrome is an interesting prospect to address in future clinical trials, given that the thromboembolic mechanism in these patients has not been fully elucidated.

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