DIAGNOSIS OF SENSORY-PREDOMINANT CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: THE EXPERIENCE OF OUR CLINIC

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ABSTRACT — We present our experience in diagnosis of sensory-predominant chronic inflammatory demyelinating polyneuropathy (SP-CIDP), which utilizes unique approach, including computerized pallesthesiometry and thermosensomtery, transcutaneous oxymetry and stabilometry. We strongly emphasize the connection between Herpes viridae infection and SP-CIDP. Attention to chief complaint of patient and multimodal testing of superficial and deep sensation is accentuated. We suggest our approach to diagnosis for wider utilization considering high prevalence of SP-CIDP in general population. We believe, that implementation of our diagnostic approach in clinical medicine will clarify epidemiology of SP-CIDP. Our system helps practitioner in differential diagnosis and further management of patient with SP-CIDP.

KEYWORDS — sensory-predominant chronic inflammatory demyelinating polyneuropathy (SP-CIDP), diagnosis, human.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) belongs to a group of dysimmune neuropathies. The prevalence of CIDP varies between 0.5 in children [1] and 9.0 per 100000 of population in adults [2, 3, 4]. In Krasnoyarsk krai the prevalence of CIDP is significantly higher – 25.5 per 100000 of population [5], which is thought to be due to climate and higher prevalence of immunodeficiency among the population of Siberia. Risk factors of CIDP are immunodeficiency, diabetes and neurotrophic viruses [6]. Antigens which trigger autoimmune response are currently not known [4]. Interestingly, *Herpes viridae* infection is found in 80% of CIDP cases [5]. Cellular and humoral immune response play major role in pathogenesis of CIDP, where demyelination transforms into axonal degeneration of peripheral nerves [4, 7]. CIDP has diverse clinical presentation. Classic CIDP is characterized by sensorimotor symptoms, including hyporeflexia, sensory disturbances in distal segments of extremities with muscle weakness appearing in later stages of disease [1]. Usually, the diagnosis of CIDP is not difficult. However, sensory-predominant CIDP (SP-CIDP) is frequently underdiagnosed in outpatient clinic. The reason for this is that patient usually doesn't have any complaints during early stage of disease. Underdiagnosis of SP-CIDP and lack of adequate therapy results in further progression of symptoms and worsening of patient's condition. Approximately 50% of polyneuropathies of unknown cause may be attributed to SP-CIDP [8]. Diagnosis suggested to be established by electromyography (EMG), nerve biopsy, nerve ultrasound and cerebrospinal fluid (CSF) testing [1, 9]. Diagnostic criteria for CIDP are not strictly specific in these methods, but they verify the presence of demyelination. Unfortunately, demyelination is universal process of damage to nervous system, including peripheral nerves. Because of this, these methods have low specificity for CIDP. Similar presentation may occur in diabetic polyneuropathy, Charcot-Marie-Tooth disease type 1, paraneoplastic and other forms of polyneuropathies. Furthermore, nerve biopsy and CSF testing are highly invasive methods which are only done in the setting of inpatient departments. Thus, development of new diagnostic approach to SP-CIDP in outpatient clinic, which utilizes modern non-invasive neurophysiological testing, is needed. Furthermore, implementation of new diagnostic battery will improve epidemiologic data on CIDP.

There are two stages in the diagnosis of SP-CIDP in our clinic.

STAGE 1: PHYSICAL EXAMINATION

New approach to diagnosis of SP-CIDP was developed in the Neurological Center of Epileptology, Neurogenetics and Brain Research of the University Clinic of the Krasnoyarsk State Medical University (UC KSMU) in 2013. It is suitable for initial diagnosis of SP-CIDP with utilization of new algorithm. The registry of patient with SP-CIDP has data collected for 5 years. As of now, there are 176 patients in the database. We expect significant increase in patients after implementation of new neurophysiological algorithm of SP-CIDP diagnosis in other clinics.

Analysis of subjective symptoms is done during first visit of patient to UC KSMU. The presence of


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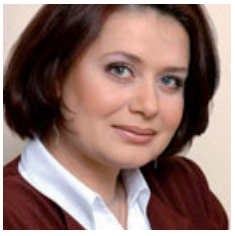
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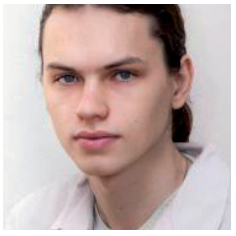
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distal paresthesia, numbness in hands and feet, pain in gastrocnemius muscle is noted. These symptoms may be suggestive of other demyelinating polyneuropathies. Chronic *Herpes virus* infection (e.g. orofacial and genital herpes) must be noted as well, including family history of such infections; 28% of patients from our study have had familial cases of *Herpes virus* infection. In our clinic the multimodal evaluation of superficial and deep sensation is available. Interestingly, there is a hyperesthesia in form of "gloves and stockings" during testing of pinprick sensation with Wartenberg pinwheel. Distal hypesthesia is less common. Thermosensation is evaluated with thermoesthesiometer (Tip-Term). Electrothermometer allows measuring of local temperature on the surface of skin. Distal hypothermia is commonly found in polyneuropathies. Touch sensation is tested with monofilaments. In most cases of SP-CIDP the symptoms are initially confined to distal segments of extremities. Sensitive ataxia of varying degree may be present during testing of balance.

STAGE 2: NEW NEUROPHYSIOLOGICAL ALGORITHM OF SP-CIDP DIAGNOSIS

Computerized pallesthesiometry (CPa) is developed for evaluation of thick Aβ myelinated fibers of distal peripheral nerves, which are responsible for conduction of vibrosense [10, 11]. The vibration is provided in following frequencies – 8, 16, 32, 64, 125, 250 and 500 Hz. Reduced vibrosense may be revealed in preclinical stage of SP-CIDP, when tuning fork test is negative. CPa is a screening method of diagnosis. If SP-CIDP is suspected, computerized thermosensometry (CTh), stabilometry, transcutaneous oxymetry (TCOx) and nerve conduction studies (NCS) follows (fig. 1).

Thinly myelinated fibers of peripheral nerves are responsible for conduction of thermosense. CTh is designed for evaluation of thermosense in distal parts of upper and lower extremities (hands, forearms, feet and calves). Thermodynamic test is carried out in order to evaluate sensation of cold and warmth, as well as pain thresholds for these stimuli. Cold dysethesia is revealed in 70% of patients with SP-CIDP. Furthermore, slight reduction in sensation of cold and warmth is also characteristic for SP-CIDP. It must be noted, that similar findings may also be present in diabetic polyneuropathy [5].

Sensitive ataxia is evaluated during stabilometry. Rhomberg test on stabilometer is helpful in determination of type of ataxia; it may differentiate between sensitive, cerebellar, cortical and vestibular ataxias.

Our algorithm features TCOx, which measures the amount of transdermal oxygen in lower extremities. TCOx was previously used for evaluation of patients with diabetic foot [12]. Reduction of transdermal oxygen in the presence of SP-CIDP may suggest impairment of peripheral nervi vasorum of lower extremities and may hint on the involvement of autonomic nerve fibers.

Beside aforementioned tests we also do NCS for patients with suspected SP-CIDP. NCS usually reveals axonal demyelina-

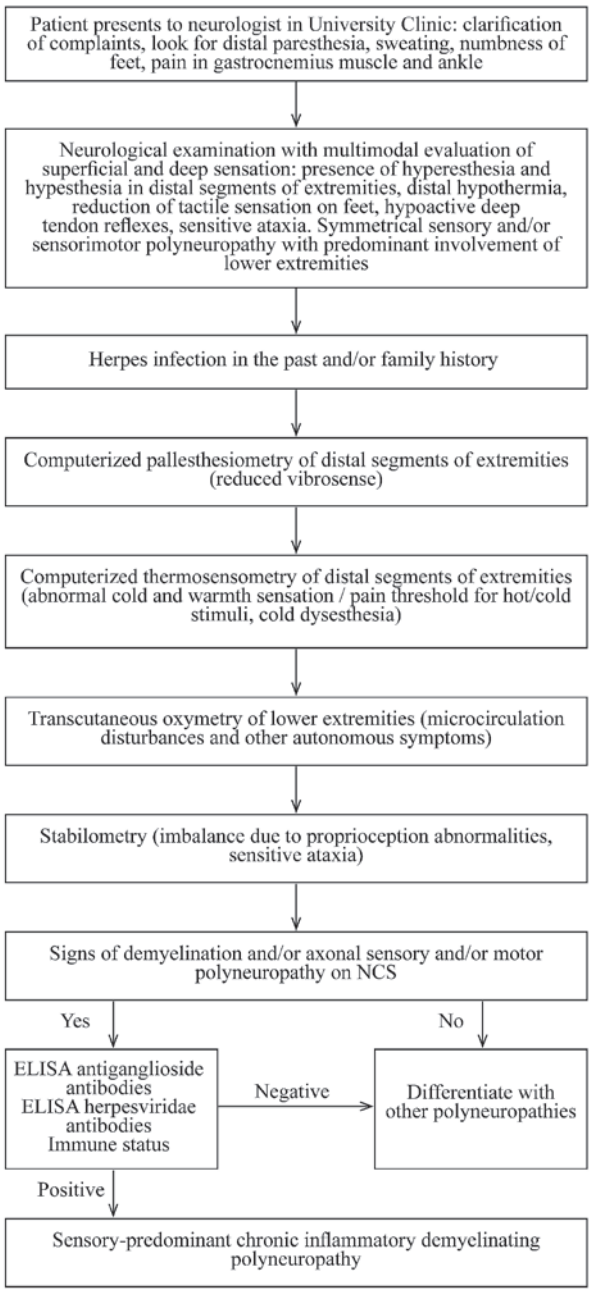

Fig. 1. *Diagnostic algorithm of sensory-predominant in our university*

tion of motor (in the absence of motor weakness) and sensory fibers. Similar results provided in Chin et al. article [8].

Enzyme-linked immunosorbent assay (ELISA) for IgG and IgM to herpesviridae viruses is done for every patient, as well as immunological status tests [5]. For some patients, antiganglioside antibodies testing is indicated.

If the diagnosis of SP-CIDP is confirmed, immunoglobulin treatment and antiviral therapy is initiated.

Case report

31-year-old female patient complains of headache, feeling of weightlessness and earfullness with bouts of blurred vision for several seconds, weight gain since last year and irregular periods, elevation of blood pressure up to 130/... mmHg, which is accompanied by vertigo and gait disturbance, slight elevation of body temperature up to 37° C. Headache is dull and monotonous, located in frontotemporal region, which is present every day starting two months ago.

Medical history is noted for frequent nasal and labial herpes since childhood.

Patient also complained of auditory hallucinations presenting as if someone is calling her name, which started in 2004 and were accompanied with inadequate behavior and ambulatory automatism. Patient's colleagues called ambulance and she was hospitalized. Patient does not remember this occasion. In autumn of 2013 patient started to hear conversation of a man and woman upon waking up. These hallucinations were regularly experienced for up to two times a month.

Patient's mother occasionally experienced visual hallucinations and was evaluated for epilepsy with negative results. She also had orofacial herpes. Her father had relatives with epilepsy.

Patient links worsening of her condition with recent change of residence – patient lived in Norilsk for 2 years before moving back to Krasnoyarsk in May 2013. After that, patient had irregular periods and rapid weight gain, as well as appearance of bilateral xanthomas on lower eyelids.

Patient has artistic job, which is sedentary (working on PC) and accompanied with stress.

Also, patient's history is notable for car accident in 2010, in which patient sustained head trauma which manifested as retrograde amnesia and spatial disorientation for 2 months. Concussion was diagnosed and patient was treated.

Patient was listed for annual anti-influenza vaccination but because of slightly elevated body temperature she was unlisted and undergone an evaluation for tuberculosis, which was negative.

On physical examination in the outpatient clinic, the patient is oriented, in no acute distress, well developed and overweight. Her skin is moderately moisturized, with xanthomas on lower eyelids bilaterally. There are no edemas. Her eyes are reddish with scant serous discharge. Submandibular lymph nodes are enlarged, no tenderness. Tonsils are enlarged. Nasal breathing is mildly obstructed. Her blood pressure is 90/60 mmHg. Diffuse enlargement of thyroid gland of 2–3 degree is noted.

On neurological examination in UC KSMU revealed facial asymmetry presenting as uneven eye

slits and nasolabial folds on the left side. Mild constitutional exophthalmos was noted. Mild myopia. Eye movements were slightly restricted in extreme horizontal deviations bilaterally. Horizontal nystagmus with moderate oscillations was present, which slightly exacerbated upon left gaze. Reduced pinprick sensation was present on left side of face. Mild tongue deviation to the left. Palmomental reflex was present bilaterally. Muscle tone was reduced in all extremities. Deep tendon reflexes were normoactive and symmetrical. Finger-to-nose test and heel-to-shin test were performed with mild ataxia. Rhomberg's test is negative. Hypesthesia was present in distal segment of arms and hyperesthesia was revealed in distal segment of feet. Gait is normal. Arches of foot were high bilaterally. Sweating was observed in hands and feet. No meningeal signs were found.

Complete blood count test revealed lymphopenia and monocytosis. Immunogram revealed elevation of cytotoxic cells and reduction of CD16. ELISA found IgG antibodies against herpes simplex viruses (HSV) 1 and 2, as well as cytomegaloviruses (CMV) and Epstein-Barr viruses (EBV).

Visual evoked potentials (VEP) demonstrated signs of axonal demyelination of optic nerves on pre- and postchiasmal region, more prominent on the ride side.

Brain magnetic resonance imaging (MRI) with utilization of "epilepsy" program revealed shrinking and deformation of right hippocampus (mesial temporal sclerosis). Video-EEG-monitoring demonstrated prolonged interictal focal epileptiformic activity in right temporal lobe.

Patient underwent evaluation using our new algorithm of neurophysiological diagnosing of SP-CIDP, which included CPa, CTh, stabilometry, TCOx and NCS. All tests were done on upper and lower extremities.

NCS ("Neurosoft", Ivanovo, Russia) revealed significant slowing of conduction in both sensory and motor fibers of medial nerve bilaterally, as well as in sensory fibers of tibial and peroneal nerves bilaterally.

Stabilometry showed disturbance of general posture with involvement of visual proprioceptive system (Fig. 2).

CTh (thermodynamic test with identification of pain threshold to cold and warm stimuli) (MBN, Moscow, Russia) did not reveal any harsh abnormality in temperature sensation on upper extremities. However, moderate elevation in pain threshold for cold stimuli was noted, which was progressively getting more pronounced in proximal segments of extremities. Temperature sensation, both for cold and warm stimuli, was slightly reduced on readings from lower extremities. Pain threshold for cold stimuli was markedly elevated in lower extremities. These data is suggestive of cold dysesthesia, signifying mild damage to non-myelinated and thinly myelinated fibers of distal segments of lower extremities.

CPa (MBN, Moscow, Russia), read from styloid processes of ulnar bone, revealed reduction of vibrosense at frequencies 16, 32, 125, 250 Hz on the left side and at 125 and 500 Hz on the right side. This data can be interpreted as mild damage to thickly myelinated Aβ fibers of distal segments of upper extremities (Fig. 3).

CPa (MBN, Moscow, Russia), registered from ankles, showed slight reduction of vibrosense in wide range of frequencies on both sides with a more pronounced reduction at frequencies 250, 500 Hz on both sides and at 64, 125 Hz on the right side. This can be interpreted as moderate to severe damage to thickly myelinated Aβ fibers of distal segments of lower extremities (Fig. 4).

TCOx ("Radiometer TCM4", Copenhagen, Denmark) revealed slight reduction at all points of interest on the right side and at the level of foot on the left side.

Finally, the following diagnosis was made: "Chronic persisting mixt-herpes (HSV-1, 2, CMV, EBV) infection presenting as labial, nasal herpes with frequent exacerbations, currently in remission (last relapse on December 2013). Mild autonomous, sensory type of CIDP, newly diagnosed. Mild sensitive ataxia. Mild chronic bilateral inflammatory axonal demyelinating mononeuropathy multiplex of optic nerve, newly diagnosed. Chronic parainfectious (herpes mix-infection: HSV-1, 2, CMV, EBV) limbic encephalitis presenting as mesial sclerosis. Symptomatic temporal epilepsy of moderate frequency with simple sensory seizures (in form of auditory and olfactory hallucinations) and ambulatory automatisms, newly diagnosed. Moderate lateral ventricular asymmetry. Diencephalic syndrome with abnormalities in lipid and carbohydrate metabolism. Hypertension. Phobic anxiety disorder. Secondary immunodeficiency with constant hyperthermia and disruption of T-cell mediated immunity.

CONCLUSION

This diagnostic program was used in 147 patients with SP-CIDP. They were all revealed starting since 2012 until September 2014. Chronic *Herpes viridae* infection and secondary immunodeficiency was revealed in the majority of patients, which confirms connection between SP-CIDP and *Herpes viridae* infection. Distal paresthesia and numbness, accompanied with distal hypothermia are the main symptoms of SP-CIDP. CPa, CTh, stabilometry, TCOx and NCS are strongly

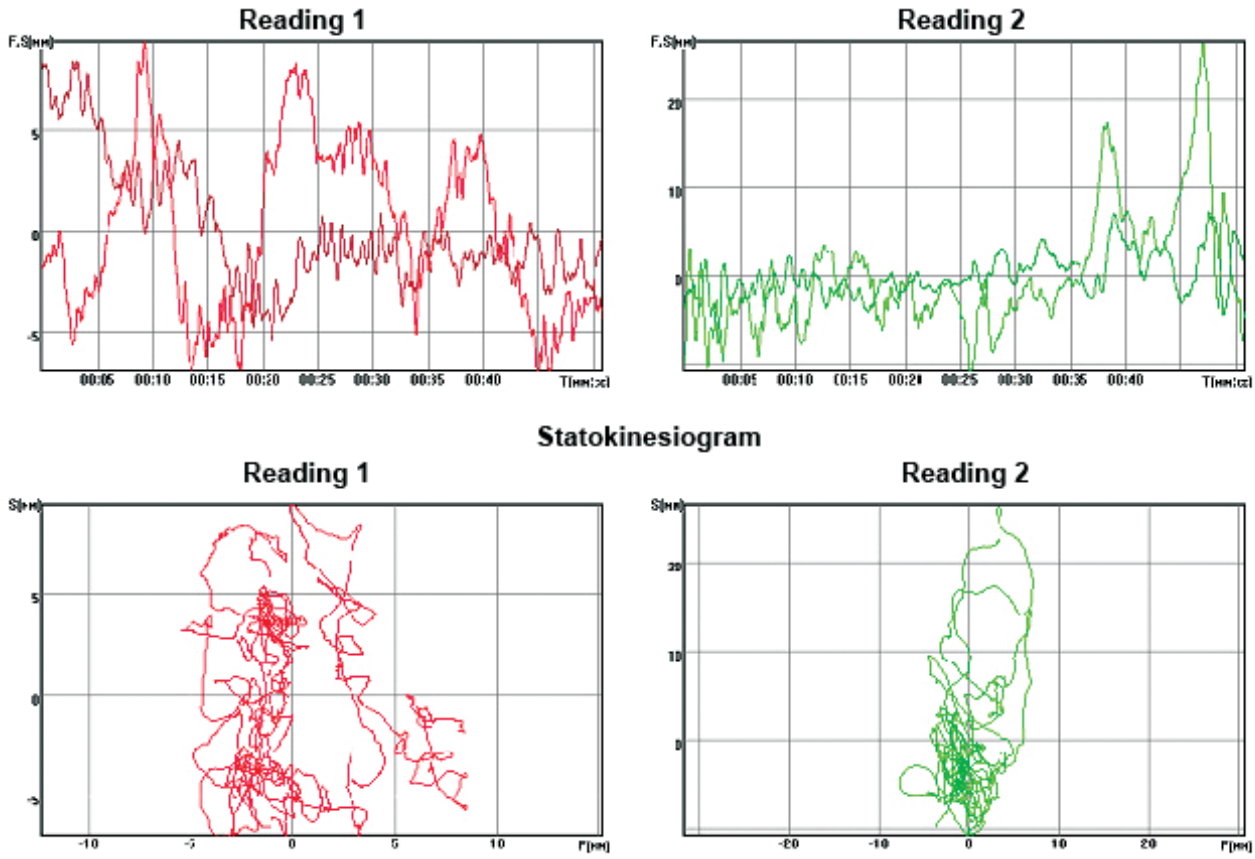

Fig. 2. Stabilometry (case report) – in Rhomberg's position (EU standard) with eyes open (A) and eyes closed (B)

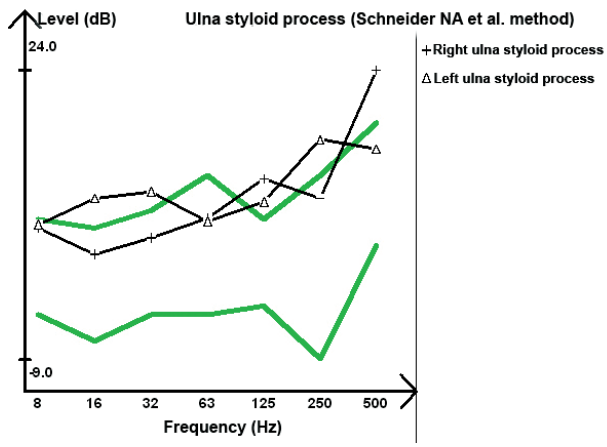

Fig. 3. Computerized pallesthesiometry (CPa), readings from styliod process of elbow bone – reduction of vibrosense on the left at following frequencies: 16, 32, 125, 250 Hz and on the right – 125, 500 Hz (Green line – reference range, black line – actual readings)

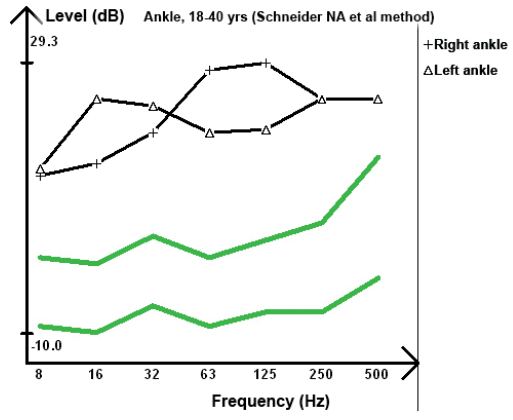

Fig. 4 . Computerized pallesthesiometry, readings from ankles – slight reduction of vibrosense in wide range, with more pronounced reduction at 250, 500 Hz bilaterally and 64, 125 Hz on the right side (Green line – reference range, black line – actual readings)

indicated in evaluation of SP-CIDP. In our experience, these tests were very helpful in confirming SP-CIDP. Furthermore, wide utilization of these tests may alter the epidemiological data available.

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