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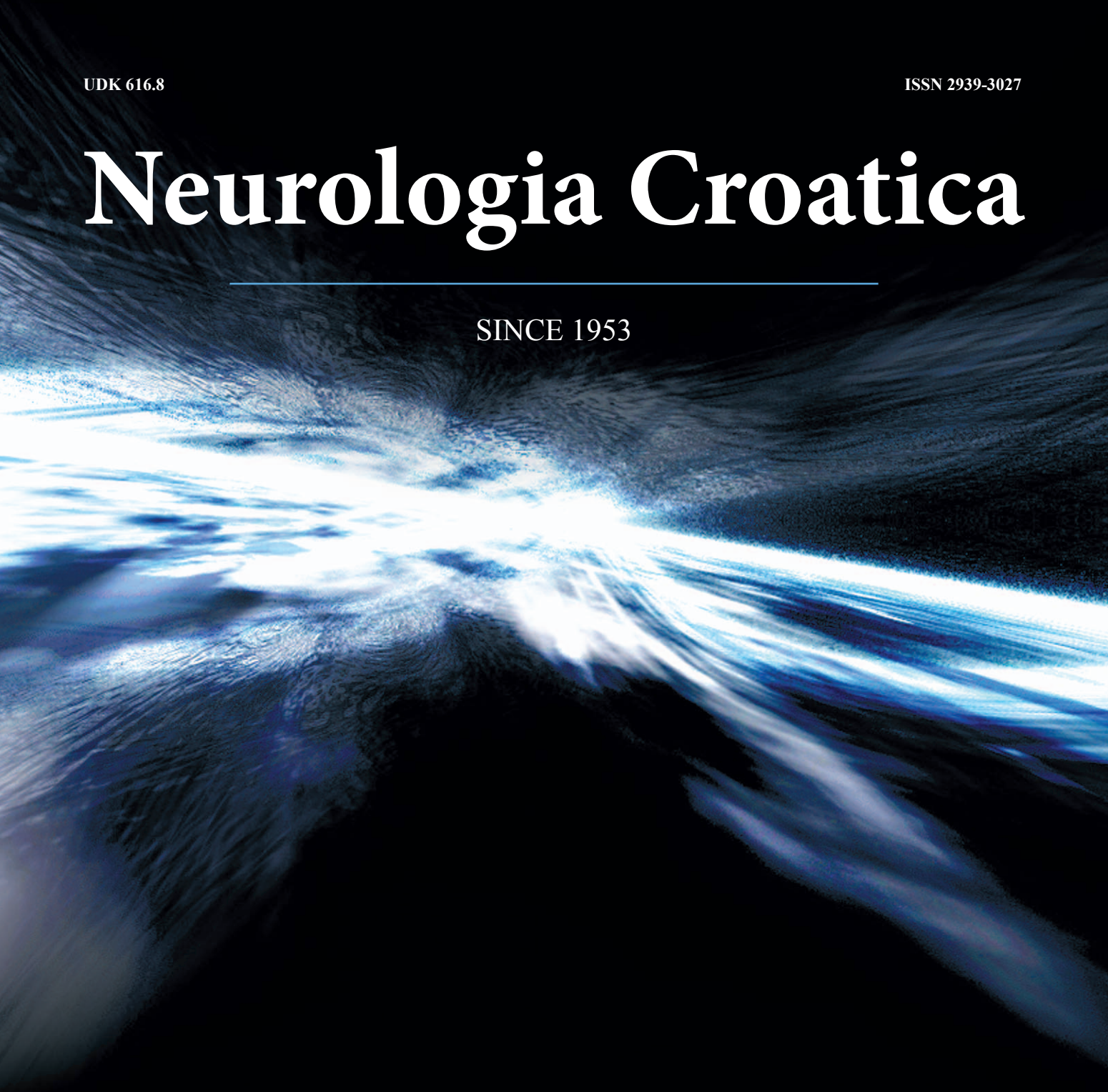

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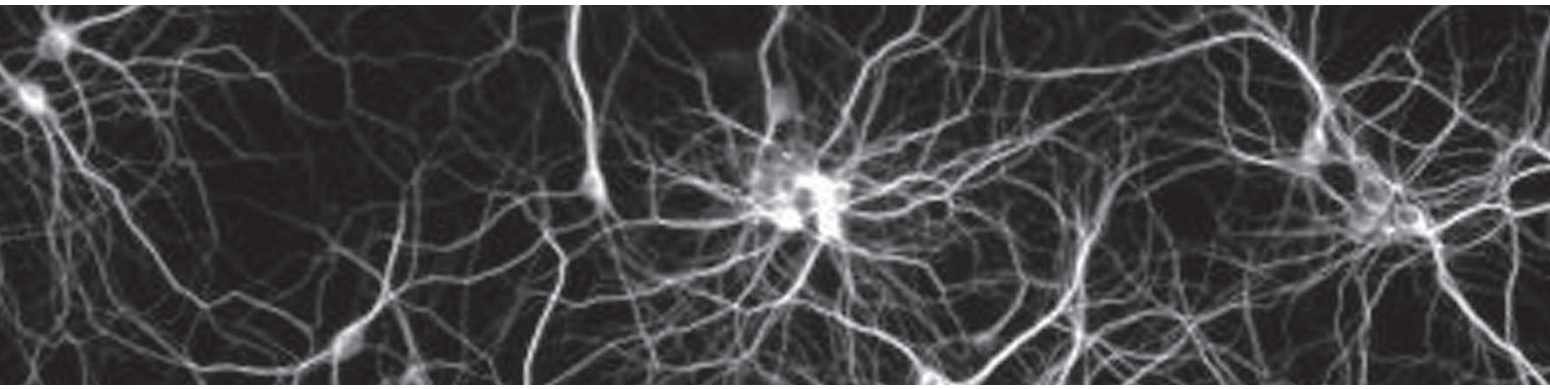
Contents



Editorial

Dear Readers and Colleagues,

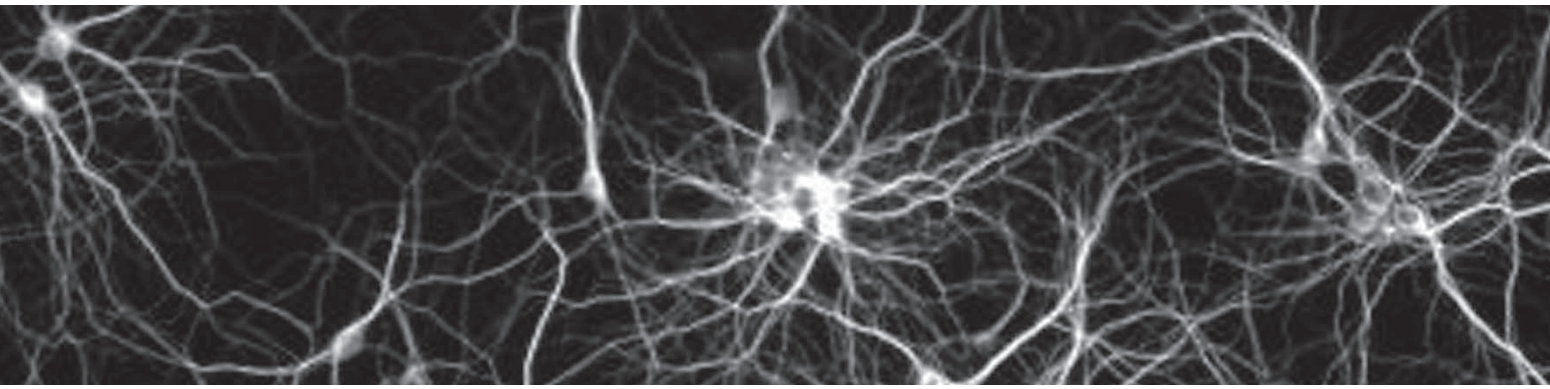
Welcome to the first issue of Neurologia Croatica in 2024.

In this issue, we bring you an interesting paper about the diagnostic pathway in patients with a non-specific presentation of neurosarcoidosis, emphasizing the role of magnetic resonance imaging. Furthermore, we present the study results investigating the effect of different forms of highly active disease modifying therapy on T lymphocyte values in persons with multiple sclerosis. The importance of having a broad differential diagnosis to avoid misdiagnosis in patients suffering from Parsonage-Turner syndrome is presented as an educational case report.

In memoriam is dedicated to Ana Sotrel, MD, the expert in the field of neuropathology, whose scientific contribution and enthusiasm for research in neurological diseases are well known worldwide.

We hope you will enjoy reading this issue and invite you to submit your educational reviews, preliminary results of your research, and interesting case reports to our journal.

Mario Habek
Magdalena Krbot Skorić



Engorgement of deep medullary veins as a key diagnostic MRI feature of neurosarcoidosis in an adult man: an unusual presentation of neurosarcoidosis

Krunoslav Budimir[1], Ivan Adamec[1,2], Barbara Barun[1,2], Mario Habek[1,2], Magdalena Krbot Skorić[1,3], David Ozretić[1,4], Tereza Gabelić[1,2]

ABSTRACT – *Objectives:* The objective of this paper is to present our diagnostic pathway in patients with a non-specific presentation of neurosarcoidosis (NS) without other systemic manifestations specific to sarcoidosis, with an emphasis on the role of magnetic resonance imaging (MRI). *Case description:* A 39-year-old patient who has been suffering from incontinence and paresthesia of the extremities for six years was subjected to numerous tests, including ophthalmological, radiological, neurological, and cardiological, but without clarifying the etiology of the complaints. Other anamnestic complaints during admission include instability when walking, nausea, and blurred vision. *Results:* Neurological examination demonstrated intention tremor on the extremities and on a wider basis gait resembling sensory ataxia. Cerebrospinal fluid (CSF) analysis showed an increased total number of cells, a significantly increased level of total proteins, intrathecal synthesis of oligoclonal IgG bands, and a decreased glucose value. MRI of the brain revealed patchy T2/FLAIR hyperintensities subcorticaly and periventricularly, along the frontal horn and in the putamen on the left side. The enhancement of diffusely dilated medullary veins was seen on the postcontrast images. On the SWI images, numerous small and patchy areas of signal loss were seen, which ultimately led to the diagnosis of NS in addition to a negative broad differential diagnosis. *Conclusion:* Despite numerous diagnostic meth-

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ods, in many cases, MR has a key role, especially for patients with central nervous system involvement without signs of systemic sarcoidosis.

Keywords: magnetic resonance, cerebrospinal fluid, paresthesias, sarcoidosis

INTRODUCTION

Sarcoidosis is defined as a multisystem inflammatory disease of autoimmune etiology predominantly affecting lymph nodes and lungs characterized by the pathognomonic formation of noncaseating granulomas, typically occurring in young adults between 20 and 40 years of age (1). Neurosarcoidosis (NS) refers to the involvement of the central or peripheral nervous system, and simultaneous affection of CNS or PNS with other systems is estimated to be 5%–10% of all cases. Isolated NS is extremely rare, with an approximated incidence of 0.2/100 000 (2). Clinical presentations of NS vary and result from the nature and volume of the affected tissue. The most common clinical presentations of NS are cranial and peripheral neuropathy, hypothalamic and pituitary involvement, pachymeningitis, leptomeningitis, psychiatric disorders, vasculitis, and affection of the spinal cord (3).

Diagnosis is established after an extensive diagnostic work-up, including neurological examination, neurophysiological studies, cerebrospinal fluid analysis (CSF), and magnetic resonance imaging (MRI) as the most important imaging modality. Brain or nerve biopsies are important methods in establishing pathohistological diagnosis. So far, there are no NS specific CSF biomarkers (4).

MRI features, with obligatory contrast administration, include meningeal, leptomeningeal, and vessel wall enhancement, along with brain and spinal cord parenchymal lesions. An MRI SWI (susceptibility-weighted imaging) examination is warranted in this case due to the potential association between deep medullary vein engorgement and neurosarcoidosis. Notably, recent studies have demonstrated that medullary vein engorgement was present in 7 out of 21 patients, with a higher prevalence observed in the male population (5, 6).

Treatment includes corticosteroids and immunosuppression, and for those with severe disease or treatment unresponsive patients, biological therapies, including TNFα antagonists, are available.

CASE DESCRIPTION

A 39-year-old male patient has been referred for occasional episodes of right-sided limb-ascending paresthesias accompanied by nocturnal enuresis, blurred vision, and gait instability lasting for six years. Paresthesias appeared in irregular intervals and in variable parts of the affected limb, lasting never more than 30 minutes. During the patient's interview, he reported that his father has lung-affecting sarcoidosis.

There were no comorbidities present in patient's history. In 2017, an ophthalmologic assessment showed bilateral temporal and upper quadrant visual field defects due to blurred vision. The same year, a neurological examination revealed the intentional tremor with an ataxic wide-based gait. EEG, carotid Doppler ultrasound, and electromyoneurography (EMNG) findings were normal with a negative Fabry disease test. Initial brain MRI revealed an oval 11 mm lesion in the basal ganglia region corresponding primarily to a subacute vascular lesion. Following MR angiography excluded aneurysmal dilatation and stenosis. Due to the worsening of the aforementioned difficulties, the patient underwent a new diagnostic work-up in 2022. Chest x-ray findings and chest multi-slice computer tomography (MSCT), were inconclusive with doubtful left hilar lymphadenopathy. In December 2022, CSF analysis demonstrated increased total cell count (107, out of which 91 were small lymphocytes), significantly elevated levels of total proteins (1,55 g/L), intrathecal oligoclonal band synthesis, and slightly decreased levels of glucose (2,10 mmol/L). In addition, CSF analysis ruled out *Borrelia burgdorferi*, *Listeria*, *Morbillivirus*, *Rubella*, VZV, and HSV1 infection and showed elevated intrathecal chitotriosidase levels (CSF to serum chitotriosidase ratio Q 3,30). This was the only spinal tap that was performed and analysis of flow cytometry in CSF was not done. Autonomic nervous system testing was normal and EMNG did not reveal signs of polyneuropathy and serum calcium, chitotriosidase and angiotensin-converting enzyme (ACE) were normal. MRI depicted subcortical and periventricular areas of increased T2 fluid-attenuated inversion recovery (FLAIR) signal in-

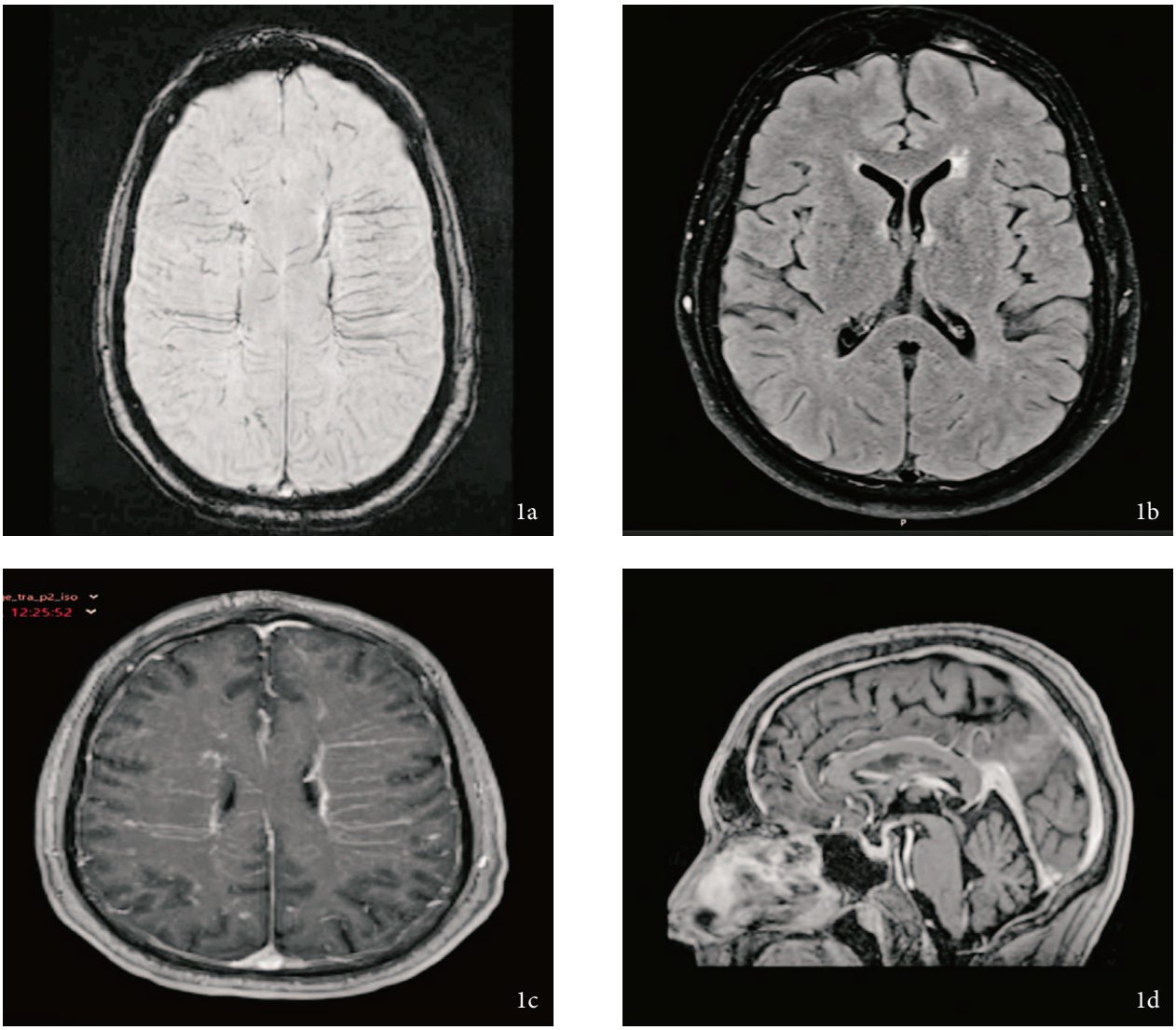

Fig. 1. *a) SWI MR shows multiple small subcortical areas of signal loss corresponding to microhemorrhage-related hemosiderin deposits and engorgement of medullary veins. b) T2/FLAIR sequence shows subcortical and periventricular hyperintensities. c) The contrast-enhanced T1-weighted MPRAGE sequence depicting diffusely dilated medullary veins. d) Sagittal plane – contrast-enhanced T1-weighted MPRAGE sequence shows contrast enhancement of the floor of the 3rd ventricle.*

tensity, also present on the left side around the anterior horn of the lateral ventricle and putamen. The postcontrast T1-weighted MPRAGE sequence revealed diffuse dilatation of medullary veins, accompanied by nodular enhancement situated predominantly in the supratentorial and infratentorial cortex as well as at the bottom of the third ventricle. Multiple small areas of subcortical signal loss were detected on the SWI sequence, located in both cerebellar hemispheres, pons, and supratentorial subcortical regions consequently to microhemorrhage-related hemosiderin deposits. MRI findings are demonstrated in Figure 1.

In January 2023, the patient underwent an endocrine evaluation where hypogonadism was detected (total testosterone 0,2 nmol/L) following gonadotropic hypophysis insufficiency. All of these findings were attributed to NS leading to the patient's methylprednisolone-based therapy prescription. A compressive vertebral fracture developed in April 2023 was suspected to be a consequence of hypogonadism and corticosteroid treatment. X-ray finding that demonstrated compressive fracture is depicted in Figure 2. Due to corticosteroids, side-effect therapy was slowly decreased, and azathioprine was introduced. In July 2023, the patient was scheduled to undergo a brain biopsy; however, the pre-biopsy brain MRI revealed disease remission, thereby confirming the effectiveness of the administered therapy and the initial diagnosis.

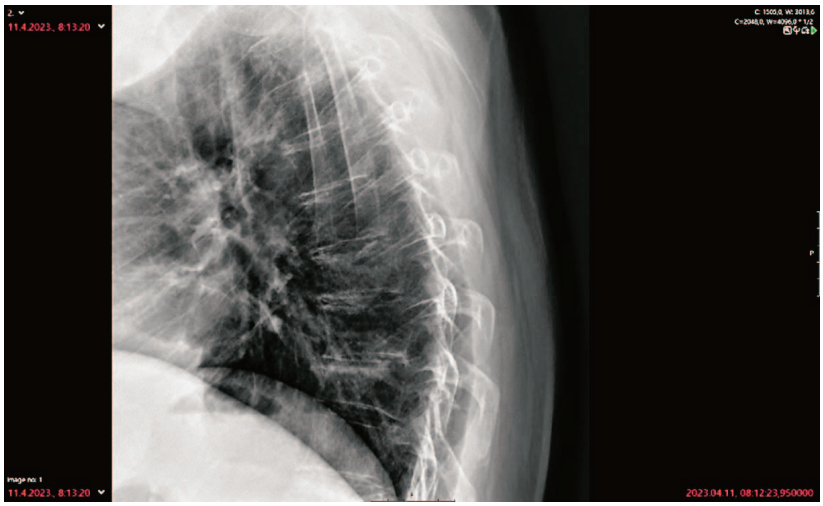

Fig. 2. *Compressive vertebral fracture due to developed osteoporosis as a complication of corticosteroid treatment and hypogonadism.*

Consequently, the patient opted to forego the biopsy procedure.

DISCUSSION

We reported a patient with an unusual presentation of NS without any specific systemic non-neurological sarcoidosis characteristics in association with negative serum biomarkers. Even though sarcoidosis is classically considered a multisystem disease, according to recent studies, approximately 10%-20% of patients with NS do not have recognizable systemic sarcoidosis (7, 8, 9). Neurosarcoidosis-related optic neuropathy commonly affects up to 35% of patients with NS and arises through several different processes (10, 11), such as subacute optic neuritis, optic perineuritis, or compressive optic neuropathy. A subacute optic neuritis, which presents identically to demyelinating optic neuritis in most respects, is after facial nerve neuropathy, the most common form of cranial neuropathy (10-14). Our patient developed blurred vision, accompanied by bilateral temporal and upper quadrant visual field defects, which are suspected to be a consequence of the chiasmal involvement due to infiltration of the hypothalamus and adjacent structures. Noted by several studies, the prevalence of peripheral neuropathy is around 10%-14% of all NS patients, usually concomitant with central neurological disorders without neurophysiological proof of peripheral involvement (15, 16). In those with manifest peripheral neuropathy, the clinical symptoms are sensorimotor or purely sensory, and the electrophysiological investigations point to an axonal pathology predominantly, although there may be conduction slowing, focal conduction block, and multifocal conduction block (15, 16). Despite normal nerve conduction findings documented in 2017 and 2023, our patient presented with occasional symptoms of sensory polyneuropathy which came along in irregular intervals lasting never more than 30 minutes. Hypothalamic and pituitary involvement has been verified on the first MRI performed in our center and confirmed through hormone analysis. Gonadotropin and thyroid insufficiency coinciding with diabetes insipidus are often identified during endocrine evaluations (17, 18). Despite a radiological response, most of these do not improve with treatment, but complete recovery still occurs (18). Significantly decreased levels of total testosterone (0,2 nmol/L) were noticed in our patient which later contributed with corticosteroids to the osteoporosis-related thoracic vertebral compressive fracture. At the onset of systemic sarcoidosis, lymphopenia is usually noticed due to the accumulation of activated T-cells at the inflammation sites (3). Also, raised serum calcium occurs in 10% of cases because of the upregulation of an enzyme that converts 25 – hydroxy vitamin D to 1,25 dihydroxy vitamin D (3). However, none of these laboratory abnormalities were found in our patient. Furthermore, elevated levels of ACE are noticed in 60% of patients with systemic sarcoidosis, but it is not a useful disease monitor biomarker since it does not always rise in relapse and is not associated with disease progression (19). A recent comparative study of ACE and chitotriosidase revealed that a raised serum chitotriosidase had a specificity of 85% in sarcoidosis (20). Not any of these serum biomarkers were detectable in our patient which

also makes this case unusual. Regarding CSF analysis, in a recent series of 128 patients with NS affecting the CNS, the median CSF protein was 0,8 (0,19 – 8,35) g/L and raised in 76% of 89 samples. The CSF to plasma glucose ratio was reduced in 81% of patients. Moreover, the median CSF white cell count was 5 (0-395) cells/μL and raised in 51% of samples. Finally, oligoclonal bands were negative in serum and CSF in 73% of this series (9,21-23). Comparatively, our patient presented with an increased CSF total cell count, significantly elevated levels of proteins (1,55 g/L), lower glucose levels (2,10 mmol/L) combined with present intrathecal oligoclonal bands, and elevated CSF to plasma chitotriosidase ratio Q (3,30). Meanwhile, those findings are nonspecific and could be also identically manifested in some other CNS conditions such as multiple sclerosis (MS) or CNS infections. MRI is the most important imaging method and in a recent series, MRI findings were abnormal in 35% of those with cranial neuropathy excluding optic neuropathy, and 100% of those with central neurological disease (11). Performing MRI imaging with paramagnetic contrast administration is essential due to its capacity to provide visualization of specific pathological conditions. Meningeal enhancement, which often corresponds with the site of the disease, including affected vessel walls, can be accurately evaluated through the utilization of this technique. Furthermore, in instances of leptomeningeal disease, the approach proves to be invaluable in delineating enhancement patterns within the adjacent cortex and white matter, thereby offering critical insights for accurate diagnosis and subsequent treatment strategies. In the context of isolated NS, the identification of vein wall enhancement and venous engorgement can provide invaluable diagnostic insights (6), especially in challenging clinical cases like this one. One recent study involving 32 patients demonstrated a sensitivity of 71.4% and specificity of 92.3% for the deep medullary vein sign which substantiates that this MR finding effectively bridges diagnostic gaps in the prior extensive diagnostic evaluation (24). However, in a very recent paper, the deep medullary vein sign was entirely absent in 14 patients with confirmed NS on histopathological examination (25). This finding complicates the diagnostic process of isolated NS, particularly when considering that venous engorgement can also be present in certain brain neoplasms, arteriovenous malformations, venous thrombosis, or Struge-Weber syndrome (26). Nonetheless, in those specified conditions, a favorable response to our therapy would not be anticipated. Our patient developed multifocal lesions on the T2/FLAIR sequence, multiple areas of signal loss on the SWI sequence, and medullary veins enhancement on the postcontrast T1-weighted MPRAGE sequence. The combination of these MRI findings, along with the patient's response to prescribed therapy for NS, played a pivotal role in confirming isolated NS.

CONCLUSION

Even though that is a rare entity, it should be kept in mind while evaluating patients with multiple non-specific CNS symptoms of longer duration. Sometimes, despite many diagnostic procedures, MRI is one of the most important methods to confirm our suspicion of NS.

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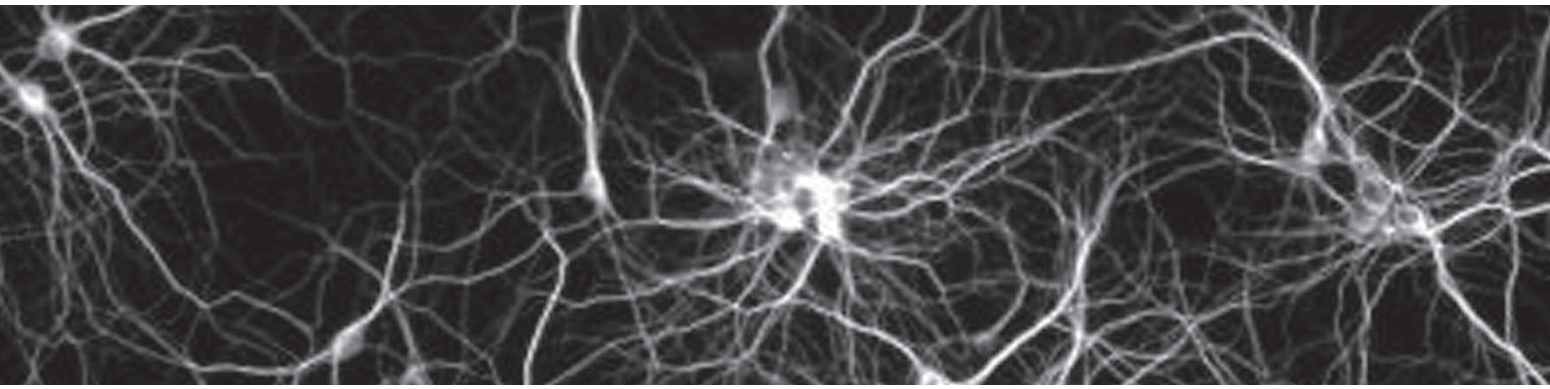

Different profiles of T cell depletion between ocrelizumab and ofatumumab in persons with multiple sclerosis

Mario Habek[1,2], Ivan Adamec[1], Tereza Gabelić[1,2], Barbara Barun[1,2], Josip Knežević[3], Antonija Babić[3], Magdalena Krbot Skorić[1,4]

ABSTRACT – *Objective:* This study aimed to evaluate changes in the levels of CD4+ and CD8+ T lymphocytes in persons with multiple sclerosis (pwMS) during the first six months of treatment with ocrelizumab or ofatumumab. *Methods:* The target population was treatment naïve pwMS starting therapy either with ocrelizumab or ofatumumab, after the first clinical presentation of relapsing-remitting MS (RRMS). Complete blood count and CD4, CD8, and CD19 lymphocyte subpopulations were evaluated at baseline and the 6-month follow-up visit. *Results:* PwMS treated with ocrelizumab had a significant drop in lymphocytes ($p=0.022$) and CD8 levels ($p<0.001$), while pwMS treated with ofatumumab had a significant rise in CD4 ($p=0.009$) and CD8 ($p<0.001$) lymphocytes at month 6. *Conclusion:* This study provides data on the opposing effect of ocrelizumab and ofatumumab on T lymphocyte values.

Keywords: multiple sclerosis, B and T cell depletion, ocrelizumab, ofatumumab

INTRODUCTION

Ocrelizumab and ofatumumab are considered high-efficacy therapies in the treatment of relapsing MS and cause profound depletion of B lymphocytes (1). Recently, it has been suggested that ocrelizumab also reduces CD4 and CD8 T lymphocytes, more pronounced compared to rituximab, another CD20 monoclonal antibody frequently used in the treatment of multiple sclerosis (2).

The aim of this study was to evaluate changes in the levels of CD4+ and CD8+ T lymphocytes in persons with MS (pwMS) during the first six months of treatment with ocrelizumab or ofatumumab. We hypothesized that both antibodies lead to similar

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depletion of B cells, with different effects on T cell subpopulations.

METHODS

PATIENTS

The target population was treatment naïve pwMS starting therapy either with ocrelizumab or ofatumumab, after the first clinical presentation of relapsing-remitting MS (RRMS).

Inclusion criteria were: 1) pwMS starting ocrelizumab or ofatumumab within six months after the first clinical manifestation of RRMS; 2) availability of complete blood count and CD4, CD8, and CD19 lymphocyte subpopulations at baseline, and at the 6-month follow-up visit. Exclusion criteria were: 1) age <18 years; 2) pregnancy; and 3) any other previous disease-modifying therapies.

The following parameters were collected for each pwMS: age, sex, site of first symptom, and Expanded Disability Status Scale (EDSS). Ocrelizumab and ofatumumab were administered as per the European Medicine Agency Summary of product characteristics for each medication (4, 5).

FLOW CYTOMETRY

The four-color flow cytometry analysis of peripheral blood was carried out by staining the cells with appropriate fluorochrome-conjugated antibodies (CD19-APC [clone SJ25C1]), CD8-FITC [clone SK1], and CD4 -PE [clone SK3]) in two separate tubes. The FACS Lyric (*BD Biosciences, San Jose, USA*) was used for the acquisition of samples, and data were analyzed by FACSuite ver1.2 software (*BD Biosciences, San Jose, USA*). The absolute count of lymphocyte subsets (per μL of blood) was obtained by using absolute lymphocyte count (ALC) derived from the hematological analyzer Sysmex XN-3000 (*Sysmex Corporation, Kobe, Japan*).

SATISTICAL ANALYSIS

Statistical analysis was performed with the IBM SPSS v25 software. The data distribution was tested with the Kolmogorov-Smirnov test. The differences between qualitative variables were tested with the chi-square test. According to the distribution, differences between the two groups for the quantitative variables were tested with the parametric independent sample t-test and non-parametric Mann-Whitney test. Differences between two timepoints (baseline and month 6) were determined with the paired t-test and Wilcoxon signed ranks test. P-values less than 0.05 were considered significant.

RESULTS

We enrolled 36 consecutive pwMS treated with ocrelizumab and 30 pwMS treated with ofatumumab. The baseline demographic and laboratory characteristics of both cohorts are presented in Table 1. PwMS treated with ofatumumab had lower baseline levels of lymphocytes, CD4 and CD8 lymphocyte subpopulations.

PwMS treated with ocrelizumab had no change in leukocyte (6.75 (5.28-7.80) vs 7.35 (5.98-7.90), p=0.201) or neutrophil counts (4.31±2.05 vs 4.61±2.09, p=0.376), however, we observed lower lymphocyte counts six months after the treatment initiation in comparison to baseline values (1.83±0.60 vs 2.12±0.59, p=0.005). There was a significant reduction of CD19 lymphocytes between baseline and month 6 (0 (0-2) vs 223 (161-255), p<0.001). When looking at the T-cell subpopulations, there was no change in CD4 lymphocytes (920±320 vs 979±322, p=0.202), while there was a significant reduction in CD8 lymphocytes (456±180 vs 516±188, p=0.004) six months after the treatment initiation.

PwMS treated with ofatumumab had no change in leukocyte (6.73±1.64 vs 6.87±1.53, p=0.527), neutrophil (4.21±1.25 vs 4.42±1.34, p=0.376), or lymphocyte counts (1.75±0.52 vs 1.71±0.45, p=0.628) six months after the treatment initiation. There was a significant reduction of CD19 lymphocytes between baseline and month 6 (0 [0-1] vs 183 [129-245], p<0.001). When looking at the T-cell subpopulations, there was a significant increase in both CD4 lymphocytes (896±323 vs 789±263, p=0.004) and CD8 lymphocytes (494±196 vs 408±147, p=0.002) six months after the treatment initiation.

In order to account for the baseline differences in T lymphocyte subpopulations between the two groups, we calculated the percentage changes in each of the studied parameters between month 6 and baseline which are presented in Figure 1. PwMS treated with ocrelizumab had a significant drop in lymphocytes and CD8 levels, while pwMS treated with ofatumumab had a significant rise in CD4 and CD8 lymphocytes at month 6.

DISCUSSION

This study has shown different effects of ocrelizumab and ofatumumab on T cell subpopulations in

Table 1. *Demographic characteristics of the cohort.*

	OCR (N=36)	OFA (N=30)	P value
Age (years, mean±SD)	30.0±8.42	32.9±7.62	0.146
Sex (females, N %)	26 (72.2%)	21 (70.0%)	1.000
Site of first clinical presentation (N %)			0.582
ON	7 (19.4%)	4 (13.3%)	
TM	17 (47.2%)	13 (43.3%)	
BS	8 (22.2%)	6 (20.0%)	
H	3 (8.3%)	3 (10.0%)	
MF	1 (2.8%)	4 (13.3%)	
EDSS (median, IQR)	1.0 (1.0-2.5)	2.0 (1-3)	0.020
Baseline CBC			
Leukocytes	7.35 (5.98-7.90)	6.45 (5.80-7.80)	0.315
Lymphocytes	2.12±0.59	1.71±0.45	0.003
Neutrophils	4.61±2.09	4.42±1.34	0.661
Baseline flow cytometry			
CD4	979±322	789±263	0.012
CD8	516±188	408±147	0.011
CD19	231±101	198±91	0.179

OCR ocrelizumab, OFA ofatumumab, N number, ON optic neuritis, TM transverse myelitis, BS brainstem/cerebellar symptoms, H hemispheral, MF multifocal, EDSS expanded disability status scale, IQR interquartile range, CBC complete blood count

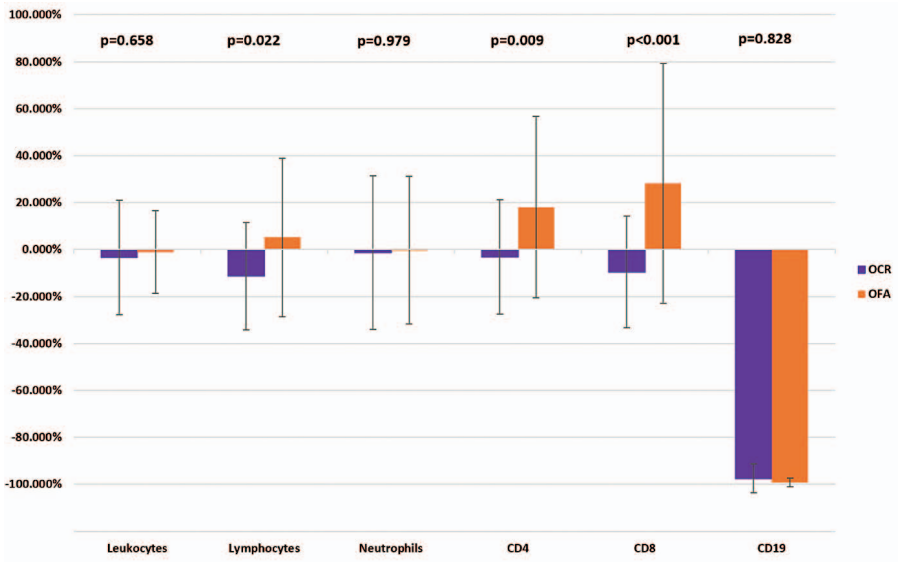

Fig. 1. *The percentage changes in leukocytes, neutrophils, lymphocytes, and lymphocyte subpopulations from month 6 and baseline between pwMS treated with ocrelizumab and ofatumumab.*

the first six months of treatment. A previous study has demonstrated that CD20-expressing T cells, which make up 20% of all CD20-expressing cells, are effectively depleted along with B cells in pwMS treated with ocrelizumab (5). A study on ofatumumab-treated pwMS did not find depletion but rather a reduction of peripheral CD20+ T cells (6). The reason behind this discrepancy and the one demonstrated in the current study on CD4+ and CD8+ cells could be the intravenous administration and the dosage of ocrelizumab that may provide a more profound deep tissue lymphocyte depletion as indicated by a longer time to CD20+ repopulation in ocrelizumab vs ofatumumab treated patients (3, 4, 7).

The difference in the effect of these two drugs on the T lymphocyte subpopulations in the current

study can have opposing implications. Previous studies have demonstrated the important role of CD8+ lymphocytes in the pathophysiology of MS. Brain biopsies of pwMS demonstrated that the T cells that were found were predominantly CD8+ tissue-resident memory cells that express CD20 with an increase of CD20+ T cell density in white matter active lesions (8). Therefore, a reduction in CD8+ cells may suggest that the clinical efficacy of ocrelizumab is not only mediated by effects on B cells (1). On the other hand, the rise in CD4+ lymphocytes observed in ofatumumab-treated pwMS could indicate an increase in regulatory T cell levels causing greater control of effector T cells, which in turn can contribute to the positive treatment effect of ofatumumab (6, 9). Currently, no head-to-head studies are comparing the effectiveness of ocrelizumab and ofatumumab, and a recent meta-analysis found a similar efficacy of both monoclonal antibodies (10).

The main limitations of this study are the short follow-up and the lack of deep lymphocyte phenotyping. However, this study provides results on the different effects of ocrelizumab and ofatumumab on T lymphocytes, and further studies with longer follow-ups are needed to examine whether this difference persists after extended treatment duration.

CONCLUSION

In conclusion, this study provides data on the opposing effect of ocrelizumab and ofatumumab on T lymphocyte values.

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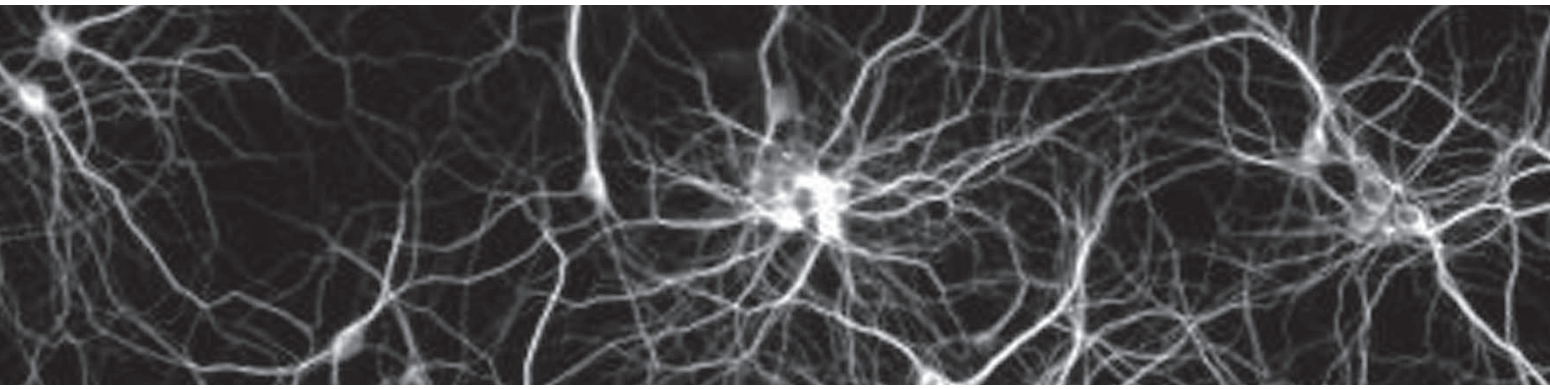

Parsonage-Turner syndrome

Borislav Radić[1], Hrvoje Bilić[2], Sarah Meglaj Bakrač[3], Antonela Blažeković[3,4], Ervina Bilić[2], Fran Borovečki[2,3]

ABSTRACT – *Objective:* Here we wanted to demonstrate the importance of having a broad differential diagnosis to avoid misdiagnosis in patients suffering from Parsonage-Turner syndrome (PTS). *Case description:* PTS is a rare idiopathic neuritis of the brachial plexus, characterized by sudden onset of pain in the shoulder and arm, followed by progressive weakness and muscle atrophy of the affected area. We present a case of a Caucasian 8-year-old boy from Croatia with acute onset of shoulder pain after viral infection recovery. The boy was treated with methylprednisolone and several courses of intravenous immune globulin. Over time, the patient developed necrosis of the right acetabulum, and corrective osteotomy was performed. At the age of 19, a neurological exam showed severe atrophy of the right shoulder muscles. *Results:* The diagnostic delay in our case was three years, showing the lack of specific tests when diagnosing PTS. Even though the patient received immunoglobulin and corticosteroid treatment, atrophy of the right shoulder muscles occurred, and his motor skills in the right arm were reduced. *Conclusion:* Since clinical presentation can reflect other pathological conditions, accurate diagnosis is difficult and oftentimes delayed. Our case illustrates the importance of including broad differential diagnosis in patients with shoulder pain for prompt initiation of an accurate therapy.

Keywords: Brachial plexus, neuralgic amyotrophy, Parsonage-Turner syndrome

INTRODUCTION

Parsonage-Turner syndrome (PTS), also known as neuralgic amyotrophy or brachial plexitis, is a rare neurological disorder first described by Dreschfeld in 1887. Multiple reports followed to describe the condition with Parsonage and Turner (1948) being the most important ones (1). The syndrome can vary greatly in presentation and nerve involvement. It is usually characterized by the sudden onset of acute severe pain in the upper arm and shoulder girdle followed by progressive weakness leading to flaccid paralysis and muscle atrophy of the affected area. It is usually unilateral, affecting the

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dominant side, although it can appear on both sides of the body. Even though the etiology of the idiopathic form of the disease is not yet fully understood, it is believed that most cases are due to an autoimmune response to an infection (i.e., smallpox, influenza, coxsackievirus, cytomegalovirus (CMV), human immunodeficiency virus, SARS-CoV-2 virus) (2, 3). Vaccination, surgery, pregnancy, certain medical procedures, or strenuous exercise can also lead to the development of PTS (4-7). The other, hereditary form is an autosomal dominant inherited neuralgic amyotrophy usually caused by mutations in the SEPT9 gene on chromosome 17 (8).

The estimated incidence of PTS is 1.64 per 100,000 people per year (4), mainly affecting the male population aged 20 to 60 years. Since clinical presentation can reflect other pathological conditions, accurate diagnosis is difficult and oftentimes delayed (9). The diagnostic workflow includes nerve conduction studies (NCS), electromyography (EMG), magnetic resonance imaging (MRI), and/or X-ray. Treatment is symptomatic and includes analgesics, corticosteroids, and physiotherapy. The estimated recovery rate is 75% to 90% within 2 and 3 years from symptom onset, respectively (4, 10).

CASE REPORT

An 8-year-old boy was admitted to the hospital for a tingling sensation in his right forearm and three weeks of constant pain in the right upper arm. The pain occurred after an episode of pharyngitis treated with amoxicillin and clavulanic acid. Neurological examination revealed impaired convergence of the left eye, brisk tendon reflexes of the right extremities, and a positive Oppenheim and Chaddock signs on the right site. All other aspects of the neurologic exam were normal. Laboratory workup results (sedimentation rate, complete blood count, renal and liver function tests, coagulation tests, antinuclear antibodies, rheumatoid factor, serum protein electrophoresis, copper levels, and antiganglioside antibodies) were within normal range. Cerebrospinal fluid (CSF) analysis was also within normal values. *Borrelia burgdorferi*, CMV, *Toxoplasma gondii,* and *Bartonella* serology tests were negative, while the Epstein-Barr virus test (EBV) showed positive IgG and negative IgM titers. Other microbiological findings were negative. Molecular genetic analysis for hereditary neuropathies (CMT1A/HNPP) was negative and no duplication or deletion in the PMP22 gene was found. The HLA-B27 test was also negative. EMG indicated a moderate loss of motor neurons in the foot and reinnervation potentials in the right deltoid muscle. NCS showed reduced compound muscle action potentials (CMAPs) and prolonged distal latency bilaterally in the right axillary and peroneal nerve with normal motor velocity. X-ray imaging of the sacroiliac joints showed bilateral sclerosis. Skeletal scintigraphy was normal. MRI of the brain and cervical spine showed no abnormalities. Con-

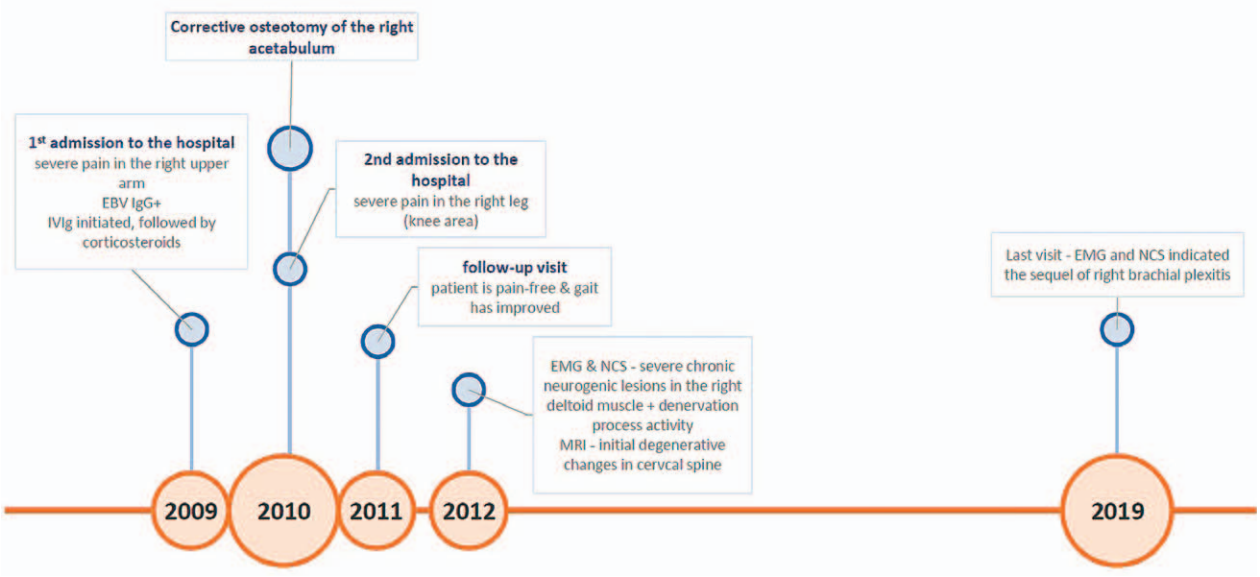

Fig. 1. *Timeline chart showing key points of the Parsonage-Turner Syndrome Case Report (EBV – Epstein-Barr virus; EMG – electromyography; IVIg – intravenous immune globulin; MRI – magnetic resonance imaging; NCS – nerve conduction study). Bubble Chart Timeline Template © 2017 by Vertex42.com*

trast computed tomography (CT) of the base of the neck, chest, abdomen, and pelvis indicated enlarged lymph nodes in the axillary and inguinal regions, with no other pathological changes. An infectious disease specialist was consulted and found no signs of acute infectious disease; the workup indicated only a past EBV infection. The patient was initially admitted under the diagnosis of an atypical form of Guillain-Barré syndrome, due to the pain and tingling sensation in his right arm. Therapy with intravenous immune globulin (IVIg) was initiated at a dose of 0.4 g/kg for 5 days and was continued with methylprednisolone orally at a dose of 64 mg daily with dose tapering. A year later the patient was readmitted to the hospital with a neurological exam showing severe atrophy of the right shoulder muscles and limited abduction and anteflexion in the right shoulder joint. The patient was given a second course of IVIg (0.4 g/kg) and was discharged with steroid therapy.

Three months later, he was readmitted to the hospital with complaints of severe pain in the right leg (knee area). The third course of IVIg was administered (0.4 g/kg), followed by the fourth course a month later. The patient was taking methylprednisolone orally until the age of 10 when it was stopped due to persistent pain in the right hip. X-ray diagnostics revealed aseptic necrosis of the right hip, and corrective osteotomy of the right acetabulum has been performed. At the age of 12, the patient's EMG and NCS findings showed a severe chronic neurogenic lesion in the right deltoid muscle, with signs of denervation, distal conductive block, slowed conduction velocity in the right axillary nerve, and proximal conductive block in the right peroneal nerve with prolonged distal latency on the right peroneal nerve. MRI of the cervical spine showed initial degenerative changes of C2-C3 and C3-C4 intervertebral discs without signs of disc herniation and with no signal changes in the spinal cord. MRI of the right brachial plexus showed hyperintensity and irregular thickening of lateral and posterior branches, a finding that may correspond to chronic inflammatory changes of nerve tissue. Also, muscle atrophy of the right shoulder girdle was noted. The patient continued with physical therapy and visited a pediatric neurologist on a regular 6-month basis. Figure 1 presents a timeline chart of key points in the boy's treatment.

During the last visit at age 19, EMG and NCS indicated the sequel of right brachial plexitis. A neurological exam showed severe atrophy of the right shoulder muscles (Fig. 2, 3), diminished deep tendon reflexes in the right upper extremity, and very limited abduction (to about 40 degrees) of the right arm in the shoulder.

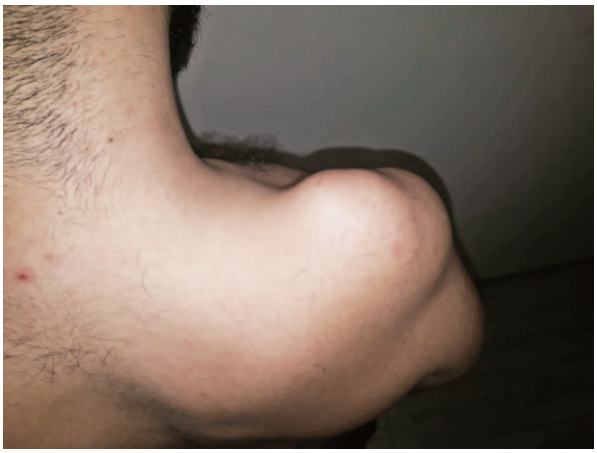

Fig. 2. *Deltoid atrophy*

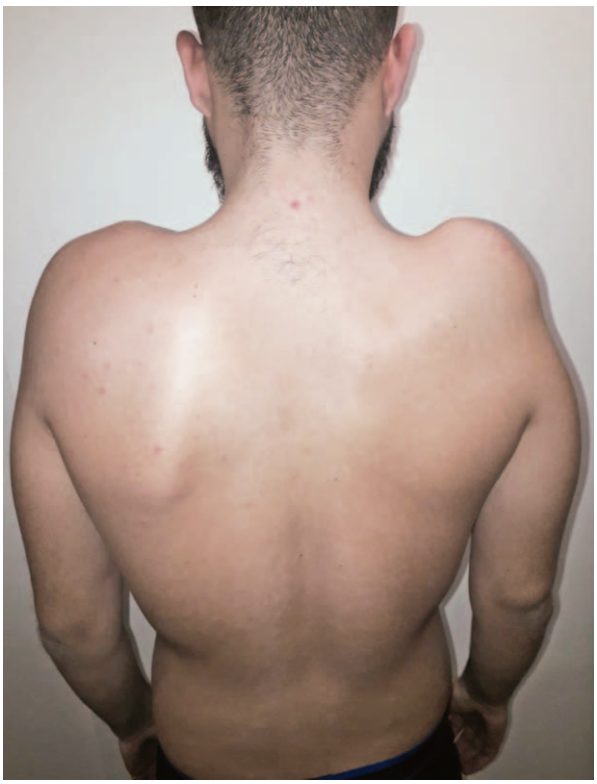

Fig. 3. *Supraspinatus and infraspinatus atrophy*

DISCUSSION

PTS is predominantly a clinical diagnosis with the classic presentation of abrupt onset, intense, unilateral shoulder girdle pain, often nocturnal at onset, with subsequent and progressive muscle weakness and varying levels of sensory abnormalities. Although the pathophysiology is not completely under-

stood, it is likely immune-mediated as there is a high reported incidence (up to 50%) of preceding infections (11). A pathognomonic characteristic of PTS is that pain, motor weakness, and sensory symptoms usually do not affect the same nerve distributions and that the passive range of motion is preserved. These characteristics are especially important when differentiating PTS from cervical radiculopathy and glenohumeral bursitis, which are the most common incorrect initial diagnoses (12). Although there are no specific tests to diagnose PTS, EMG, NCS and MRI scan (13, 14) can help in making the correct diagnosis. The diagnostic delay in our case was three years, showing that there is no specific test when diagnosing PTS. EMG and NCS are often decisive in making a diagnosis. In the case of shoulder pain, a broad differential diagnosis is needed to avoid misdiagnosis and treatment (15, 16).

In the case shown, pain in the right shoulder occurred after treatment of pharyngitis, indicating a preceding infection most likely of viral etiology given the positive EBV IgG titer with the finding of enlarged submandibular lymph nodes and hypertrophic tonsils. EMG indicated a moderate loss of motor neurons in the foot and a severe chronic neurogenic lesion with reinnervation potentials in the right deltoid muscle. NCS showed a lower amplitude of CMAP and prolonged distal latency in the right axillary nerve and peroneal nerve bilaterally with normal motor velocity. The patient was treated with four courses of IVIg and then continued with corticosteroids orally, for approximately one year. The steroids were discontinued due to avascular necrosis of the right hip, which was most likely a steroid therapy side effect (17).

After 12 years from the onset of the disease, complete loss of right shoulder muscles, and reduced motor skills of the right arm, the patient carries out daily life activities without significant difficulties.

CONCLUSION

Our case illustrates the importance of including a broad differential diagnostics workflow in patients with shoulder pain. PTS is an underrecognized cause of acute onset unilateral shoulder pain and paresis, often preceded by an inciting event. PTS is a medical condition that currently has no known cure. However, the symptoms of PTS can be alleviated with the use of oral steroids and physical therapy. Oral steroids have been found to be more effective when administered during the early stages of the condition, which highlights the importance of early diagnosis. If these measures fail to bring relief, surgery may be considered for patients with PTS who do not recover. A high index of suspicion should be maintained as prompt identification and management may decrease the high patient morbidity associated with this diagnosis.

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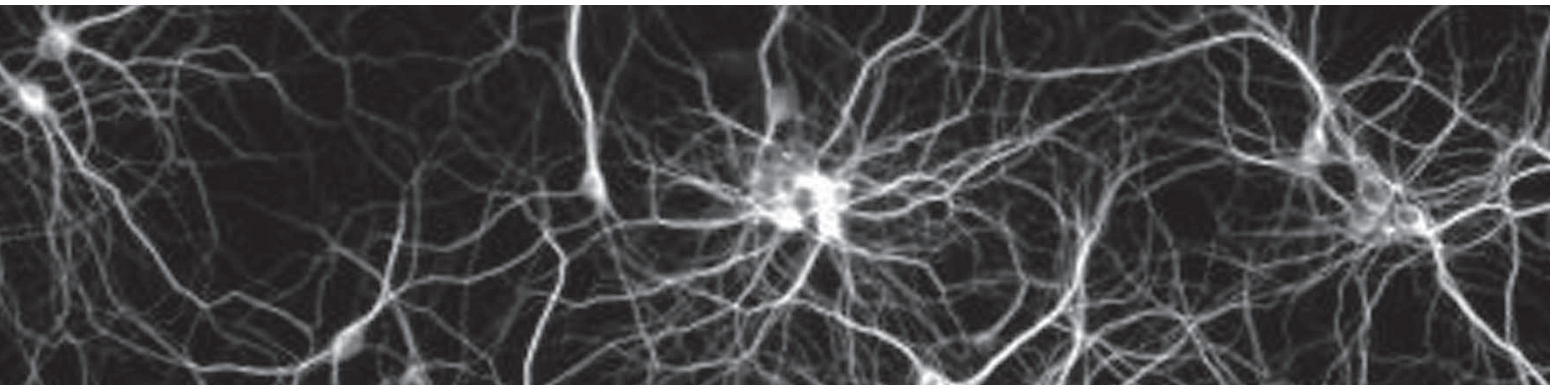


Ana Sotrel, MD

February 10, 1943 – May 22, 2022

Rebecca Folkerth, Silva Markovic-Plese, Raymond A. Sobel

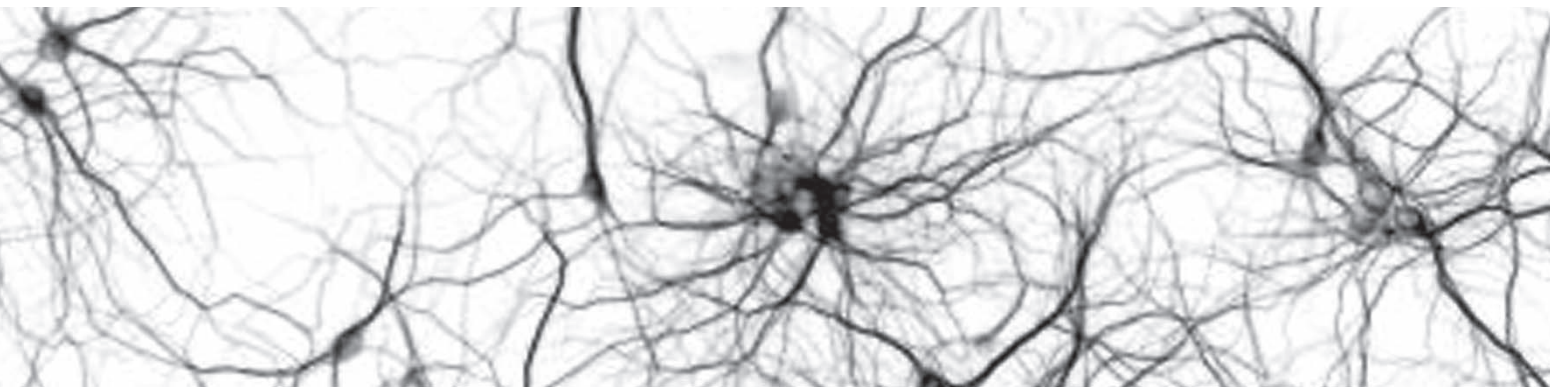
Ana Sotrel (née Jadrijevic-Mladar) was born in Sinj, Croatia. She graduated from the University of Zagreb Medical School cum laude in 1967. After a medical internship, she joined the Neuropathology Institute at the University of Zagreb. She moved with her husband Ginter and daughter Ana to the United States to pursue further education and completed pathology residency training at Rush Oak Park Hospital, Chicago. This was followed by a neuropathology fellowship at the University of Illinois, Chicago. Ana joined the pediatric neuropathology group at Boston Children's Hospital in 1975 where she worked with Profs. E. Tessa Hedley-White and Floyd H. Gilles, who inspired her to gain comprehensive knowledge in pediatric neuropathology. She joined the faculty at Harvard Medical School where she was known as an outstanding and passionate clinical neuropathologist and teacher. She moderated monthly interesting case conferences that attracted neuropathologists from Boston and surrounding areas. This regular gathering was a highlight for senior practitioners and trainees alike as we spent Saturday mornings sharing our puzzling or classical cases in a relaxed collegial environment. Detailed notes from those fascinating cases remain in the files of many of us!

Dr. Sotrel's publications from her time at the Beth Israel Hospital and the Eunice Kennedy Shriver Center were primarily focused on pediatric neuropathology case reports, many still unsurpassed in their cogent observations. She was a member of the Childhood Brain Tumor Consortium, contributing to the staging of pediatric infratentorial neu-

roglial tumors. Her broad research interests included the neuropathology of infectious complications of HIV/AIDS, rare childhood syndromes, epilepsy, and Huntington disease. Dr. Sotrel subsequently worked at Northwestern University, Columbia University, and the University of Miami Florida, from which she retired. She trained numerous fellows and residents to whom she passed her emphasis on careful analysis along with her enthusiasm for research in neurological diseases.

She adored her daughter Ana, who is a practicing architect in New York City. She loved long beach walks, enjoyed political arguments and was very much loved by her family, as the most inspiring and helpful member.

Ana passed away in Jacksonville, Florida, on May 22, 2022, at the age of 79. She is survived by her daughter Ana, multiple nieces and nephews, and other family members and friends. Her incisive take on neuropathology (and life!) will be missed.



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Books

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Chapter in a book

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions.

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