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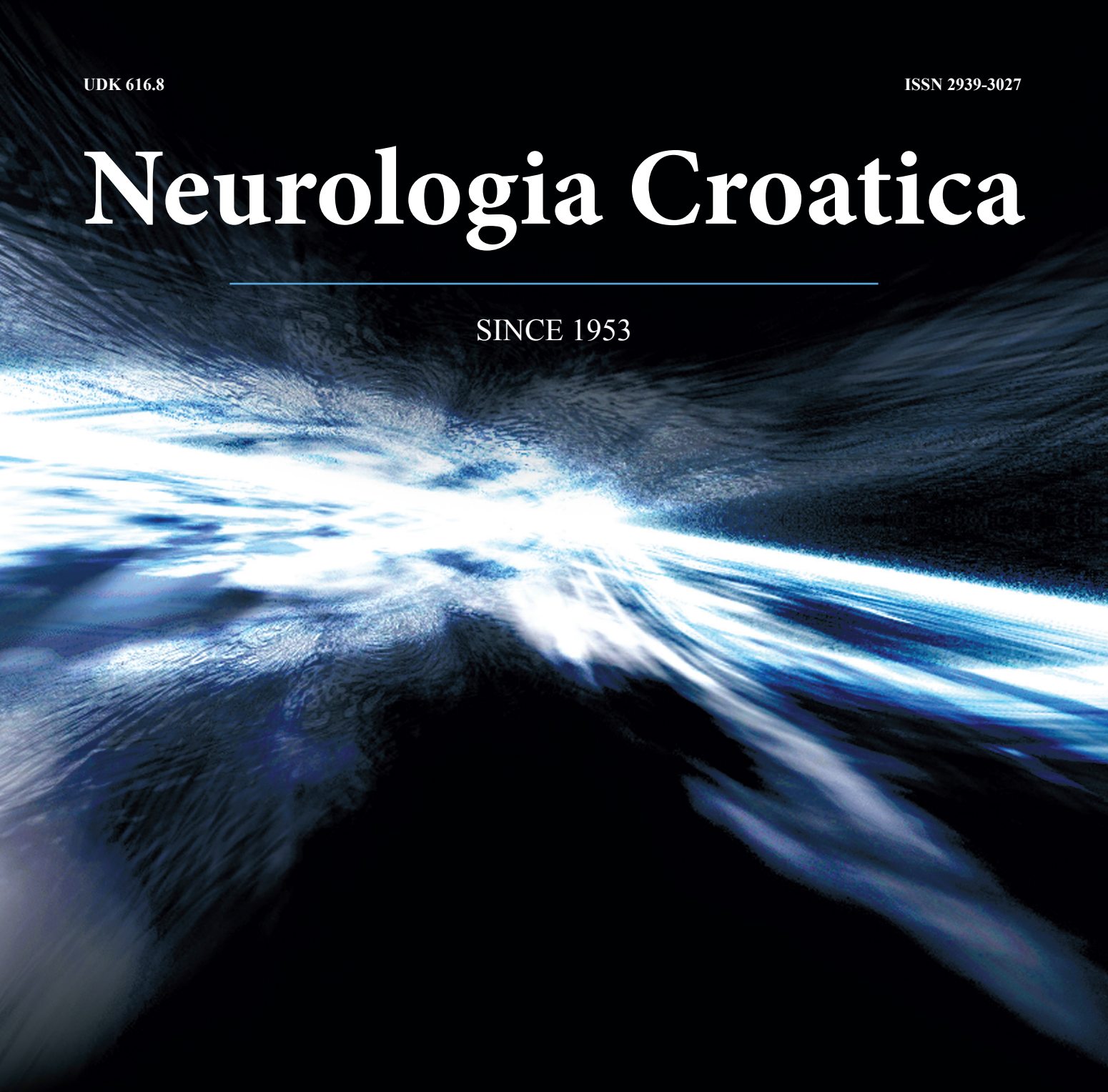

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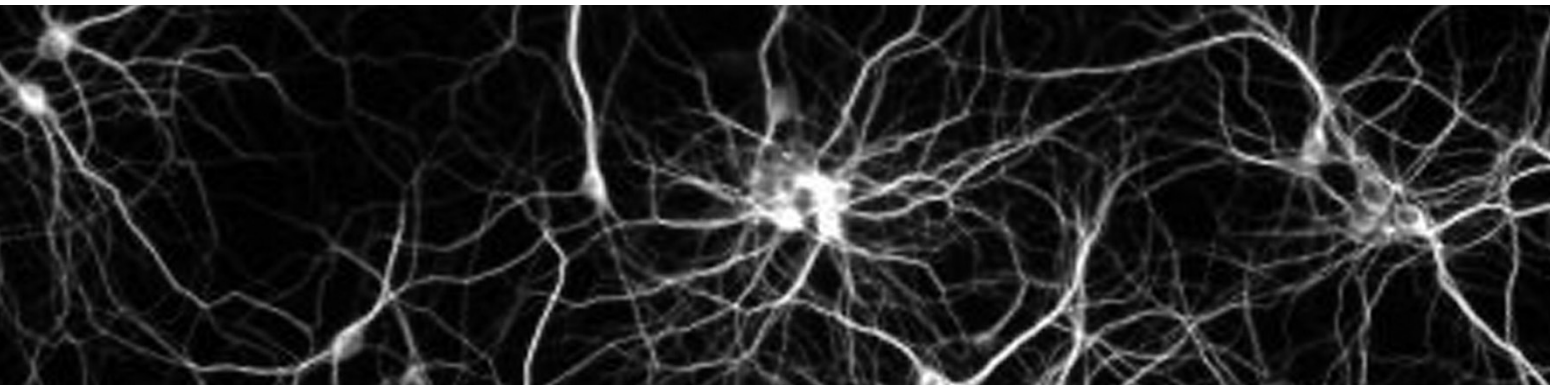


Editorial

Dear Readers and Colleagues,

It is my great honour to welcome you to the first issue of the journal "Neurologia Croatica" in 2023. Although the journal had experienced stagnation with reduced publications in the recent years, we are aware of the fact that this journal was very important for the past of neurology in Croatia and it is our wish that it will also be an important part of the neurological future in its new and improved edition.

As one of the major goals of the editorial board is to enhance the international visibility of our journal, we will continue to publish articles only in English, with the online submission and review system. Reviewers for the journal are international experts from the specific field of the neurology and broader, and with their clinical and scientific expertise they ensure the maintenance of the quality of the published material.

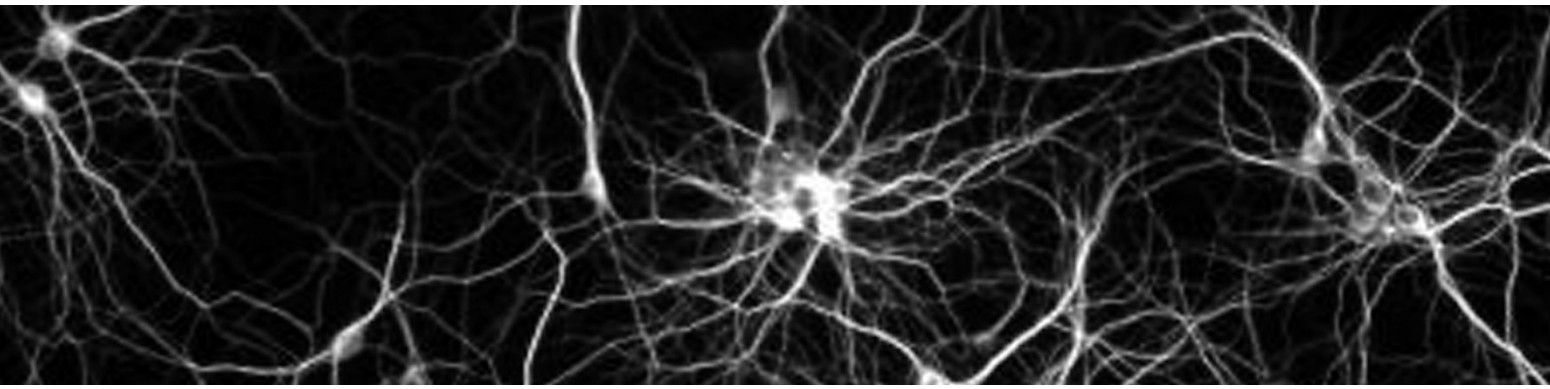
This issue provides insight in different areas of neurology. Readers will be informed about interesting case reports from the daily clinical practice, introduced to the usage of the new technology in diagnostical procedures, learn more about different treatments and therapies related to specific neurological diseases and get insight into a case of a patient with the specific novel gene mutation.

Articles contained in this issue were presented at the 8th Croatian Neurological Congress with international participation, which was held from 26-30 April 2022 in Rijeka, Croatia.

We hope that you will find this issue of "Neurologia Croatica" interesting and that it will encourage you to submit manuscripts for future editions.

Magdalena Krbot Skorić
Deputy Editor

Mario Habek
Editor-in-Chief



Autologous hematopoietic stem cell transplantation in a person with highly active relapsing-remitting multiple sclerosis

Ana Abičić[1], Borislav Radić[2], Ivan Adamec[3,4]

ABSTRACT - *Objectives:* To present a patient treated with autologous hematopoietic stem cell transplantation (AHSCT) for relapsing-remitting multiple sclerosis (RRMS) and to discuss the role of AHSCT in the treatment of RRMS. *Case description*: A 36-year-old patient was diagnosed with RRMS at the age of 19 and treated with AHSCT at the age of 21, after failure of the first-line disease-modifying therapy (DMT). Before the treatment, multiple relapses caused disability accumulation resulting in Expanded Disability Status Scale (EDDS) score of 6.0. *Results*: An improvement in EDSS score from 6.0 to 3.0 was noted following the transplantation, with low clinical and magnetic resonance imaging activity during the 15 years of follow-up. No serious adverse events or complications of the treatment were noted, and the patient has been ambulatory without support to date. *Conclusion*: AHSCT is a treatment option for highly active RRMS refractory to DMT. Careful patient selection and balance between risks and benefits is crucial for successful treatment.

Keywords: hematopoietic stem cell transplantation, immune reconstitution, multiple sclerosis, relapsing-remitting

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated disorder affecting the central nervous system in which focal lymphocytic infiltration leads to damage of myelin and axons (1). In about 80 percent of patients with MS, the first phase of disease is characterized by bouts of acute exacerbation of disease activity, defining relapsing-remitting multiple sclerosis (RRMS) (1). Highly active RRMS is defined with one or more of the following characteristics: two or more relapses with incomplete recovery in the ongoing year, no response to treatment with one or more disease-modifying therapies (DMTs) for at least one year, more than two brain magnetic resonance imaging (MRI) studies demonstrating

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new lesions or increase in the size of the lesions in T2, lesions that enhance with gadolinium despite treatment, and the Expanded Disability Status Scale (EDSS) score of 4.0 at five years of onset of the disease (2,3).

Several studies have assessed the use of autologous hematopoietic stem cell transplantation (AHSCT) as a possible treatment for MS and current evidence indicates that the patients who are most likely to benefit from this treatment are young and ambulatory, with high disease activity (4,5).

CASE DESCRIPTION

A 36-year-old female patient was diagnosed with RRMS in June 2005, after admission due to weakness of the left limbs. She experienced her first episode of neurologic disability in May 1997, at the age of eleven, with tingling in the feet and problems with walking. Two years later, she had a second episode with hypoesthesia, right leg weakness, and difficulty walking. The third relapse occurred in November 2000, with weakness in the left limbs and gait instability, and the fourth relapse occurred two years later with weakness of the right leg. The patient was started on interferon beta in August 2005, however, two new relapses occurred after three and seven months with residual neurologic disability. The neurologic examination at that time revealed spastic triplegia, the patient was ambulatory with unilateral assistance, with an EDDS score of 6.0 (2). Due to high disease activity despite treatment with interferon beta, the patient was offered AHSCT treatment.

In July 2007, she was admitted for stem cell transplantation. Hematopoietic stem cell (HSC) mobilization was done on the first day with an injection of cyclophosphamide 2 g/m2 of body surface area, adding an injection of 2-mercaptoethane sulfonate sodium (MESNA) dose of 2 g/m2 to it. Intravenous fluid (0.9% saline) and MESNA were alternately given on day 5, (a total of 3L/m2 with 2 g/m2 MESNA). Furosemide was applied intravenously in a dose of 20 mg. From the second day onwards, injections of 10 μg/kg granulocyte colony-stimulating factor (G-CSF) (300 μg twice daily) along with injections of methylprednisolone 1mg/kg/day were given until absolute neutrophil count (ANC) of 1,000/μL was reached. The next step was a collection of stem cells, performed on the day on which ANC crossed 1,000/μL. The collection was done on an apheresis machine. A total of 2-2.5 times of blood volume (70 ml/kg of body weight) was processed and autologous HSCs were collected. CD34 and CD3 positive enumeration was done in the harvest bag by a standard flow cytometry, and subsequently stem cells were stored in the stem cell laboratory using cryopreservation according to the standard protocol.

In October 2007, the AHSCT was performed. Conditioning was done with a high dose of immunosuppressive therapy (injections of cyclophosphamide 50 mg/kg body weight intravenously for 5 days, injections of antithymocyte globulin (ATG) 0.5 mg/kg body weight intravenously on day 6, and 1mg/kg body weight for another 5 days; injections of methylprednisolone 2 mg/kg body weight were given intravenously for 5 days). At this point, stem cell infusion was done with 3-8 × 10^6 CD34 positive cells/kg body weight with standard protocol and precautions. Post-stem cell infusion, all precautions were taken to reduce infections in view of the neutropenic state of the patient. Injection of G-CSF 5 μg/kg body weight was given until her ANC was >500/μL. Subsequently, the patient was followed-up by repeated clinical and laboratory evaluations. She experienced the common adverse events of the treatment, such as transient alopecia and nausea, but these subsided quickly. No other complications of treatment were reported.

Post transplantation, gradual neurologic improvement was noted. At follow-up one year after the AHSCT, an improvement in muscle strength and ambulation was noted, with a decrease of EDSS score from 6.0 to 3.0 (2). During the next 15 years the patient did not experience further relapses. Regular yearly brain and cervical spinal cord MRIs showed no sign of radiological activity in the following 10 years. In June 2017, one new T2 hyperintensive lesion was noted. At the latest MRI in March 2021 one new lesion in the cervical spinal cord was noted. At the last follow-up in April 2022, a neurologic examination revealed spastic tetraparesis with muscle strength 4/5, and spastic-ataxic gait, with an EDSS score of 3.0.

DISCUSSION

We report on a patient who underwent AHSCT as a treatment for RRMS with long-term clinical and radiological stability. Since the start of the use of AHSCT in the treatment of MS, there has been significant improvement in its safety, with an increase in its use in patients with highly active MS refractory to DMTs (5). Several studies showed that long-term suppression of inflammatory activity with stabilization or improvement of disability can be achieved in properly selected patients (4,5).

The ideal candidate for this treatment would be a young patient (<45 years) with recent clinical and MRI inflammatory activity and with failure of approved, high-efficacy DMT, but preferably not more than two DMTs (4). Patients with 'aggressive' disease who develop severe disability in the previous 12 months should be rapidly considered for AHSCT, even if a full course of DMT has not been completed to formally establish treatment failure (6). The disease duration should be less than 10 years and no substantial comorbidities should be present, such as pulmonary, cardiac, liver, or kidney disease. (4,6). Treatment effect is highest in patients who are ambulatory without assistance (EDSS 5.5 or less), but patients with EDSS up to 6.5 may be considered if the highest score has been reached within the preceding several months and the patient has signs of clinical and MRI inflammatory activity (4,6). In the progressive phase of the disease, the benefit/risk ratio of transplant is unfavorable, and the optimal window of therapeutic opportunity is at the early stages of disease when inflammation is predominant and disability level is low (5).

The rationale for use of AHSCT in MS is an attempt of immune reconstitution to eliminate the aberrant adaptive immune system and develop immune tolerance (4,5). However, Mondria *et al.* (7) demonstrated the persistence of lymphocyte activation markers sCD27 and intrathecal oligoclonal IgG bands in a prospective study conducted on 14 patients with secondary progressive MS who underwent AHSCT, suggesting that immunoglobulin-producing cells in the CNS compartment are insufficiently ablated (7). Clinical activity was noted in nine out of 14 patients during 36 months of follow-up (7). On the other hand, a recent retrospective study on 46 patients treated with AHSCT showed intrathecal immunoglobulin production and neurofilament light were lower after treatment with AHSCT, decreased over time and were normalized in a significant portion of patients (8).

Recommended AHSCT methodology for the treatment of MS consists of four main stages: HSC mobilization, HSC collection, immunoablative conditioning, and reinfusion of HSC (4-6). The mobilization regimen recommended by The European Society for Blood and Marrow Transplantation (EBMT) 2019 updated guidelines includes cyclophosphamide of 2–4.5 g/m2 of body surface area with MESNA and cautious hyperhydration, for bladder protection, followed by G-CSF 5–10 µg/kg daily prior to leukapheresis [6]. Conditioning regimens are classified by EBMT guidelines as high-intensity, intermediate-intensity, and low-intensity (6). Two intermediate-intensity conditioning regimens have been used most commonly in MS: BEAM (bischloro-ethyl-nitrosourea (BCNU) 300 mg/m2, cytosine-arabinoside 200/800 mg/m2, etoposide 200/800 mg/m2, melphalan 140 mg/m2) + ATG and cyclophosphamide 200 mg/kg + ATG (6). The latter one was used in the presented patient. High-intensity regimens were used in earlier trials, however, no advantages in terms of progression free survival were documented (4). AHSCT related mortality was initially high, 7.3% for the procedures performed between 1995 and 2000, but decreased significantly over the past decade to 0.2% (1/439) for those performed in the years 2012–2016 (4). Overall, the transplant related mortality was 2.0% in 829 patients transplanted for MS (4).

No evidence of disease activity (NEDA-3), meaning no relapses, no disability progression and no MRI activity, was proposed as a treatment goal in patients with RRMS (4,5,9). As shown in a meta-analysis by Sormani *et al.* (9), NEDA-3 values achieved in most AHSCT studies are higher than those reported with conventional DMTs. In the HALT-MS study, in which 25 patients with RRMS were enrolled, the proportion of patients with disability progression after AHSCT was <10% at 3 years (10). A prospective study published in 2016, which enrolled 24 patients with MS treated with AHSCT, demonstrated complete suppression of all detectable CNS inflammatory activity (11). No clinical relapses occurred in any of the 23 surviving patients during up to 13 years of follow-up, and none of 327 post-transplantation MRI scans showed gadolinium-enhancing lesions (11).

A randomized clinical trial (RCT) that included 110 patients with RRMS, compared treatment with AHSCT and DMT (12). Disease progression occurred in 3 patients in the AHSCT group and 34 patients in the DMT group, with a median follow-up of 2 years (12). No deaths or serious toxicity were reported in the AHSCT group (12). DMTs included in this study were glatiramer acetate, interferon beta-1a, dimethyl fumarate, interferon beta-1b, natalizumab, fingolimod, and teriflunomide. However, alemtuzumab was not included due to safety concerns and ocrelizumab was excluded because the study completed enrollment in 2016 and ocrelizumab was not US Food and Drug Administration (FDA) licensed until 2017 (12). More evidence on the safety and effectiveness of AHSCT will hopefully be provided by five RCTs, ongoing or about to start, comparing the transplantation with the best available treatment (5).

Post transplantation, disease progression should be carefully monitored. The presented patient showed signs of MRI activity, but there are still no formal guidelines for when to resume DMT fol-

lowing AHSCT. Management of patients who underwent off-label AHSCT was studied at Massachusetts General Hospital (13). Out of seven patients, four had disease progression, so treatment with rituximab, ocrelizumab, or siponimod was initiated (13). The earliest use of a B-cell depleting therapy after AHSCT was 12 months, with no adverse effects such as opportunistic or other infections noted (13). While further studies are warranted to develop guidelines, case-based experiences remain helpful for the optimal management of these patients.

CONCLUSION

To conclude, the presented patient was treated with AHSCT for RRMS with a good clinical outcome resulting in improvement of disability and low clinical and MRI activity in the 15 years of follow-up.

Although AHSCT bears greater short-term risks than any DMT, in recent years, improved patient selection and better quality of care enabled a significant reduction of treatment-related mortality. As AHSCT is becoming a valuable treatment option, assessing the balance of benefits and risks and comparison with available DMTs is crucial for delivering the best possible care for each individual patient. Future and ongoing clinical trials will hopefully provide more evidence on the safety and effectiveness of AHSCT in MS, comparing the transplantation with high-efficacy DMTs.

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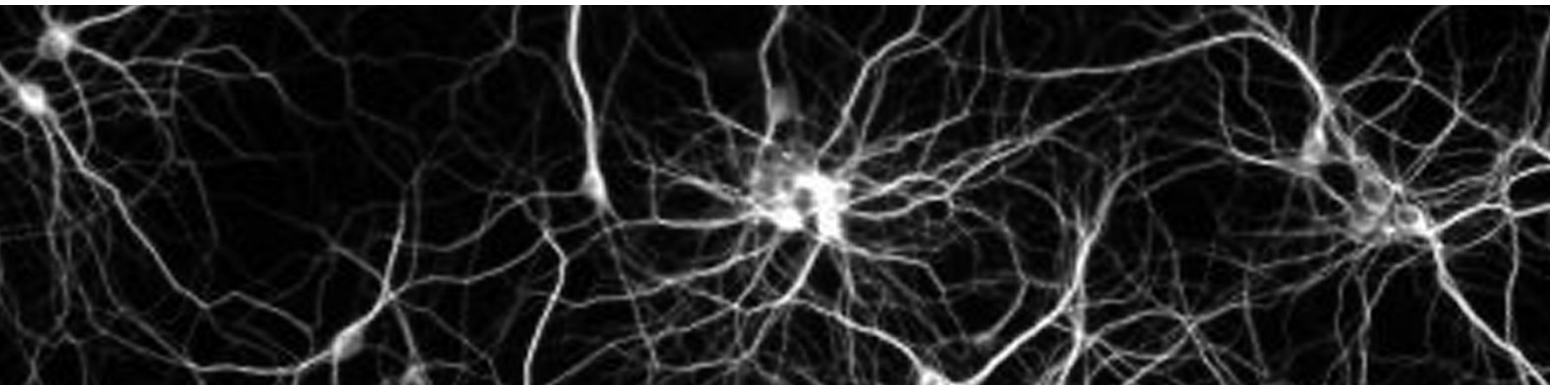

Cerebellar degeneration in a patient with suspected primary Sjögren's syndrome and unidentified antineuronal antibody in cerebrospinal fluid

Ivona Jerković[1], Nataša Milošević[1], Luka Miličević[1], Doroteja Lehpamer[1], Marina Roje Bedeković[1,2]

ABSTRACT – *Objectives:* The aim is to present a rare case of cerebellar degeneration in a patient with suspected primary Sjögren's syndrome (PSS) and unidentified antineuronal antibody in cerebrospinal fluid (CSF). *Case description:* A 52-year-old patient presented with progressive ataxia, dysarthria, and nystagmus three weeks prior to being admitted to the hospital. Upon admission, he reported walking instability, diplopia, speech impairment, and dryness of the eyes and mouth. *Results:* An extensive medical investigation ruled out vascular, neurodegenerative, infectious, metabolic, genetic, and paraneoplastic causes of cerebellar degeneration. Initial neuroimaging studies showed no brain abnormalities. Large-scale serum diagnostic tests for systemic autoimmune diseases found high antinuclear and anti-SSA antibodies associated with PSS. The CSF immunolabelled cerebellar Purkinje cells, but no specific antineuronal antibody was detected. The patient was treated with steroids, plasma exchange, immunoglobulins, and cyclophosphamide with a poor clinical response. A follow-up brain magnetic resonance imaging (MRI) performed a month and a half after the onset of symptoms demonstrated frontal lobes and cerebellar atrophy. *Conclusion:* Cerebellar degeneration in our patient could be explained by a PSS-associated antineuronal antibody. According to the latest research, the anti-SSA antibody may be a novel antineuronal antibody and its presence in the CSF may be used as a marker of CNS involvement and cerebellar degeneration in PSS.

Keywords: antineuronal antibody, anti-SSA antibodies, cerebellar degeneration, primary Sjögren's syndrome

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INTRODUCTION

Cerebellar degeneration can be a manifestation of many vascular, infectious, demyelinating, neurodegenerative, metabolic, genetic, paraneoplastic, and autoimmune-mediated disorders. While it has been reported in some patients with systemic autoimmune disorders, such as lupus erythematosus (1) and Neuro-Behcet's disease (2), it is an extremely rare presentation of primary Sjögren's syndrome (PSS), reported up to date in only a few cases (3). In 1961, Attwood and Poser described a cerebellar syndrome associated with PSS for the first time (4). Since then, there were reports of cerebellar degeneration in PSS patients with a yet unidentified antibody in cerebrospinal fluid (CSF) (5,6). The latest research on patients with paraneoplastic cerebellar ataxia proposed that the anti-SSA antibody associated with PSS, could be a novel antineuronal antibody and that its presence in CSF may be used as a marker of cerebellar degeneration in PSS (3).

We report a case of a patient with signs of cerebellar degeneration, possible PSS, and an unidentified antineuronal antibody in CSF.

CASE DESCRIPTION

A 52-year-old male patient presented with progressive ataxia, dysarthria, and nystagmus three weeks prior to being admitted to the hospital. Upon admission, he reported walking instability, diplopia, speech impairment, and dryness of the eyes and mouth. The physical exam revealed dysarthria, right peripheral facial nerve palsy, and left abducens nerve palsy accompanied by subjective diplopia when looking to the right and left, downbeat nystagmus, right and left arm dysmetria, truncal ataxia, xeropthalmia, and xerostomia.

Initial neuroimaging studies (magnetic resonance imaging [MRI], MR angiography, and MR venography) showed no brain abnormalities. The following parameters were all normal: common laboratory tests and urinalysis, thyroid hormone levels, vitamin levels, serologic and CSF PCR testing for *B. burgdorferi*, HIV, HSV, VZV, serologic antibody screening for anti-MAG, anti-ganglioside, anti-N-AchR, and anti-MuSK antibodies, serum, and CSF analysis for specific cell-surface and onconeural antibodies. The patient also tested negative for known spinocerebellar ataxia gene abnormalities (SCA1, SCA3, SCA6, SCA7) and for Creutzfeldt-Jakob disease. The labial salivary gland biopsy showed no specific pathology and Schirmer test was negative. Furthermore, thoracic and abdominal computed tomography (CT) scans and a whole-body positron emission tomography (PET) scan ruled out malignancy.

A cerebrospinal fluid analysis revealed mild pleocytosis with elevated protein levels and intrathecal synthesis of type 3 oligoclonal bands. The CSF immunohistochemical analysis showed positive fluorescence on specific cerebellum cell extract (titer 1:100). Serum diagnostic tests for systemic autoimmune diseases found high antinuclear antibody titer (ANA 1:640) and positive autoantibodies to extractable nuclear antigens (ENA) of which specific anti-SSA antibodies were highly positive (anti-Ro60 >1374.8 CU, anti-Ro52 >99.8 CU, respectfully). Follow-up MRI studies performed one month and a half after the onset of symptoms demonstrated atrophy of the cerebellum and frontal lobes.

The patient was initially treated with a high dose of methylprednisolone intravenously (1 g daily) over five days with no therapeutic answer**,** followed by a 5-day course of plasma exchange. In addition, intravenous immunoglobulins (40 g/day) were given for 5 days. Since there was no significant clinical improvement, we introduced intravenous cyclophosphamide therapy. The patient was discharged to an acute rehabilitation facility. He proceeded with cyclophosphamide treatment over the course of six months.

One year after, control laboratory findings done on regular medical checkups revealed positive serum anti-SSA antibodies (anti-Ro60 423.5 CU, anti-Ro52 21.99 CU) but in a significantly lower titer. The patient reported slow improvement in his speech and balance. A multidisciplinary decision made by neurologists and immunologists was to introduce intravenous rituximab in therapy.

DISCUSSION

We presented a patient with progressive cerebellar ataxia, which requires a wide diagnostic approach. Once the extensive medical investigation ruled out the cerebrovascular, neurodegenerative, demyelinating, metabolic, and infectious causes of cerebellar degeneration, two laboratory observations remained open. Serum diagnostic testing for autoimmune disorders revealed high serum ANA and anti-SSA antibodies suspecting underlying Sjogren's syndrome. Although no common antineuronal antibody was detected in CSF, a detection of

immunolabelled cerebellar Purkinje cells in CSF led to a suspicion of yet unidentified antibody causing cerebellar cell damage.

Up to date, there were only 15 cases reported of cerebellar degeneration in PSS patients to our knowledge (3, 5-18). Most patients described in the literature presented with ataxia, dysarthria, and nystagmus, accompanied by cerebellar atrophy on MRI, which were prominent clinical and neuroradiological signs in our patient. All reported patients had high serum anti-SSA antibodies and in most of them, cerebellar ataxia was the first manifestation of PSS (3, 4, 6-9, 11-17). An unidentified antibody in CSF was described by Owada *et al.* in a 55-year-old female with cerebellar degeneration and PSS (5). She presented with signs of motor weakness, severe depression, and cerebellar ataxia. They concluded that the detected antibody is associated with PSS and may be the cause of cerebellar symptoms in their patient. While a similar finding was also reported by Terao *et al.* (6), in other reports on cerebellar degeneration and PSS, the antineuronal antibody was not detected at all (12, 15), or the testing for common antineuronal antibodies was not performed (16-18). The clinical response to immunosuppressive treatment in reported cases was variable. Five patients were only treated with steroids (5-8) and in some of them, immunoglobulins and cyclophosphamide were introduced into therapy (14-17). Two patients had a significant clinical improvement to steroids alone (5, 6), two of them were successfully treated with a combination of steroids and cyclophosphamide (14, 17), and one patient improved to immunoglobulins alone (10). Other reported patients either showed minimal clinical response to treatment or no improvement at all.

The exact pathological mechanism of cerebellar degeneration in PSS is still unclear. Some studies implicated that Ro52 protein could be a major target for an antineuronal antibody in PSS patients with cerebellar degeneration (3, 19, 20). A recent Japanese experimental study which was done on murine cerebellar tissue sections found that Ro52 (TRIM21) protein is highly expressed in cerebellar Purkinje cells (3). Moreover, some research showed that anti-Ro52 antibodies directly inhibit the function of Ro52 proteins, leading to cerebellar Purkinje cell death and cerebellar atrophy (21, 22). In 2021, a positive anti-SSA antibody was found not only in serum but also in the CSF of a 36-year-old male patient with cerebellar degeneration and newly diagnosed PSS (3). This has supported some previous findings on intrathecal production of anti-Ro52 antibody (19) and led to the assumption that anti-SSA antibody may be an antineuronal antibody and that its presence in CSF may be used as a marker of CNS involvement and cerebellar degeneration in PSS (3).

Although all these findings led us to conclude that cerebellar degeneration in our patient may be mediated by anti-SSA antibodies associated with underlying PSS, there are some limitations in our case study. Despite clinical and laboratory findings strongly suggesting PSS, the patient did not fulfill the diagnostic criteria of the American-European Consensus Group for definitive PSS at the time of hospitalization (23). Since there is a 2-year delay in PSS diagnosis after neurological symptoms in 25%-60% of cases (24), our plan is to reevaluate findings on PSS diagnosis in the patient on a follow-up medical checkup. In addition, as our therapeutic approach would remain the same, we have not obtained CSF analysis of anti-SSA antibodies for academic purposes only. However, our goal is to implement CSF analysis for the presence of anti-SSA antibodies in a subgroup of patients with cerebellar degeneration and suspected PSS in the future.

CONCLUSION

Cerebellar degeneration in our patient could be explained by a PSS-associated antineuronal antibody. The recent literature suggests that the anti-SSA antibody may be a novel antineuronal antibody and that its presence in the CSF may be used as a marker of CNS involvement and cerebellar degeneration in PSS.

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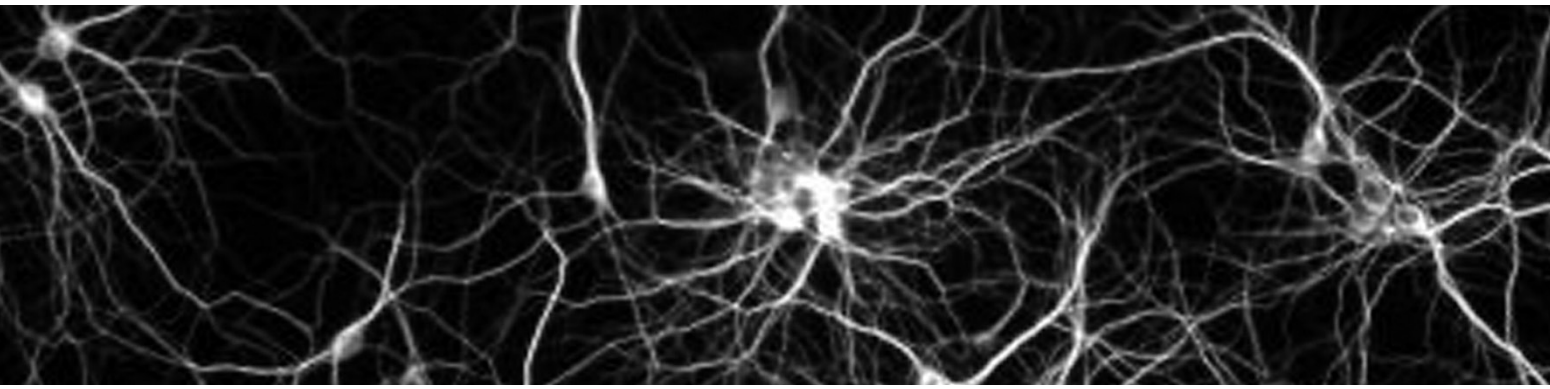

Hereditary hemochromatosis and cervical dystonia – beyond the coincidence

Luka Kusić[1], Stefan Mrđenović[1,2], Tihana Gilman Kuric[1,3], Zdravka Krivdić Dupan[1,4], Svetlana Tomić[1,3]

ABSTRACT - *Objectives*: To present a case of a patient suffering from cervical dystonia in addition to hereditary hemochromatosis, and to review the available literature regarding the link between the two disorders. *Case description*: We presented a patient with symptoms of cervical dystonia that was successfully treated with botulinum toxin. The patient also had incidentally discovered elevated levels of serum ferritin and increased transferrin saturation. Mild arthralgia of knee joints with visceral iron overload was in favor of the diagnosis of hereditary hemochromatosis. Genetic testing detected an H63D/wild-type heterozygous variant that is not usually associated with iron overload with next-generation sequencing (NGS) analysis showing no mutations in other hereditary hemochromatosis genes. A comprehensive panel for 38 dystonia-associated genes detected no mutations. The patient was treated with phlebotomy with subsequent normalization of serum ferritin and reduction of symptoms. *Conclusion*: There is a high likelihood of the correlation between the two disorders. Future studies on iron's role in cervical dystonia pathology are needed to determine their causal link.

Keywords: cervical dystonia, hereditary hemochromatosis, iron, movement disorder

INTRODUCTION

Cervical dystonia (CD) is the third most common movement disorder characterized by involuntary contractions of the head and neck muscles causing abnormal posture of the head and neck. It can be divided based on the etiology of the disease into primary and secondary or based on the abnormal position of the head and/or neck, using collum-

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caput concept, into torticollis/caput, laterocollis/caput, antecollis/caput, and retrocollis/caput patterns, and sagittal shifts (1). In primary dystonia, there are no known causes or structural abnormalities that can explain the onset of symptoms, as opposed to secondary dystonia in which there is an identifiable cause with the most common being side effects of certain medications, intoxication, head or neck trauma or structural lesions in basal ganglia due to trauma or cerebrovascular accident (2). Pathophysiology of CD is considered to be due to miscommunication between basal ganglia, cerebellum, somatosensory, motor, limbic, and visual system (3,4). Diagnosis of cervical dystonia is based upon a clinical examination with no specific abnormalities found in laboratory or brain imaging tests (5). The treatment of cervical dystonia includes pharmacotherapy with local injections of botulinum toxin (BoNT) being the most effective treatment (6,7,8).

Hereditary hemochromatosis (HH) is one of the most common autosomal recessive genetic disorders in the western world. The most common gene altered by mutation is HFE which is located on the short arm of chromosome 6 (6p21.3) with C282Y and H63D mutations being prevalent in the vast majority of patients. Mutations in the HFE gene cause an increase in the absorption of iron leading to its excess deposition in the joints, skin, liver, pancreas, heart, and some parts of the central nervous system (9). It is important to mention the existence of so-called non-HFE hemochromatosis which usually manifests as end-stage liver dysfunction due to excessive iron deposition in the liver. The most common symptoms of HH are fatigue and jaundice with cirrhosis, arthropathy, hypogonadism, hypothyroidism, and cardiac dysfunction being the most common complications of the disease. A common clinical finding includes a combination of symptoms of type 2 diabetes and diffuse hyperpigmentation of the skin giving the disorder the nickname "bronze diabetes". Diagnosis of hereditary hemochromatosis starts with the measurement of serum transferrin saturation or serum ferritin concentration, although liver biopsy and histopathological analysis remain the most sensitive and specific tests to confirm the diagnosis (10). The most effective treatment for a vast majority of patients with primary hemochromatosis remains phlebotomy (11).

In this paper, we presented a patient with CD and hemochromatosis and reviewed literature about the correlation between these two conditions.

CASE REPORT

A right-handed Caucasian male developed symptoms of CD at the age of 33. After a few years, symptoms spontaneously resolved, but ten years later appeared again. His dystonia was of mixed type with lateral sagittal shift and some component of rotation. He did not have accompanying pain or other nonmotor symptoms. His family history was negative for movement disorders. A comprehensive panel for 38 dystonia-associated genes detected no mutations. BnNT-A treatment was started and he had an adequate treatment response. Besides this, he suffers from migraine headaches. In 2015 he underwent a 1,5 T magnetic resonance imaging (MRI) that showed only vascular gliosis in periventricular and subcortical areas. In 2019 there was an incidental detection of an increased level of ferritin. A hematological workup confirmed elevated levels of serum ferritin of 1000 μg/L and slightly increased transferrin saturation of 57%. There was no family history of hereditary hemochromatosis. The patient presented with mild arthralgia of knee joints. Genetic testing detected an H63D/wild-type heterozygous variant not usually associated with an increased risk of iron overload. Abdominal MRI detected visceral iron overload with T2 signal loss with slightly increased out-of-phase sequence signal in the patient's liver, spleen, kidneys, and axial bones suggestive of hereditary hemochromatosis. Radiographic imaging of shoulder, elbow, hand, hip, knee, ankle, and foot joints detected arthrodegenerative changes that suggested hemochromatosis arthropathy. An echocardiogram showed no signs of cardiac involvement. Further evaluation detected no signs of abnormal liver function, alcoholic liver disease, chronic active hepatitis B or C infection, autoimmune hepatitis, Wilson's disease, aceruloplasminemia, or alpha 1 antitrypsin deficiency. Next-generation sequencing (NGS) analysis was performed but detected no mutations in FTH1, HAMP, HJV, SLC40A1, and TFR2 genes. He was treated with phlebotomy with subsequent normalization of his serum ferritin < 100 μg/L and reduction of arthralgia and motor symptoms.

DISCUSSION

While the relationship between hereditary hemochromatosis and cervical dystonia remains controversial, we presented yet another case in which the two disorders appear to be related in some way. Hereditary hemochromatosis usually presents it-

self with a variety of symptoms, with central nervous system (CNS) involvement considered to be somewhat rare (12). Several papers have reported a relationship between various movement disorders, including cervical dystonia and hereditary hemochromatosis (13,14,15). Kumar *et al.* evaluated a cohort of 616 HH patients for movement disorders where they found three patients with parkinsonism, chorea, and tremor. All three patients had evidence of iron deposition in the basal ganglia, with two of them having non-HFE gene mutations (13). Another cohort study on 630 individuals with p. C282Y homozygosity showed that these patients have substantial iron deposition in basal ganglia, thalamus, red nucleus, and cerebellum and confirm an increased association of movement disorders (14). Sharma *et al.* have evaluated 52 subjects with HH for movement disorders and have found in 35 of them some type of movement disorders. Authors have noticed that MRI susceptibility in specific deep gray matter nuclei correlated with movement disorder phenotypes (15). What is the possible link between iron overload and CD? Iron has a dual role in the CNS. On one side it has a fundamental role in CNS development and synaptic plasticity, and on the other side, it is linked to neurodegeneration (16,17). Both, transferrin-bound iron (TBI) and non-transferrin-bound iron (NTBI) are important for neuronal iron supply while NTBI is important for both basal synaptic transmission and long-term potentiation (LTP) (17). NTBI stimulation of reactive oxygen (ROS) and nitrogen species (NOS) lead to the activation of calcium signals through signaling cascades and resulting in gene transcription (16). In case of iron overload in the brain, NTBI can cause the production of the highly toxic hydroxyl radical that has highly detrimental effects on neurons (17). In patients with cervical dystonia, there is evidence of abnormal cortico-striatal synaptic plasticity with excessive D2 cortico-striatal synaptic depotentiation (18). There is no evidence of neurodegeneration in CD patients, but increased NTBI could impair synaptic plasticity and through this mechanism be somehow related to CD. Brain MRI scan in our patient did not show iron deposition in basal ganglia and we assumed that the concentration of the iron was not elevated enough to be toxic, but only to influence synaptic plasticity and long-term depotentiation.

While there is still no clear evidence of the correlation between these two conditions, some authors have commented on the possibility of misdiagnosing some other diseases in patients with movement disorders and HH (19). Our patient has no other neurological symptoms or signs, nor diagnostic biomarkers that will lead us to think about some other potential neurological diseases.

CONCLUSION

After careful examination of the current literature, we would argue that there is a high likelihood of a correlation between hereditary hemochromatosis and cervical dystonia. Further evaluation of iron's role in CD pathology is needed.

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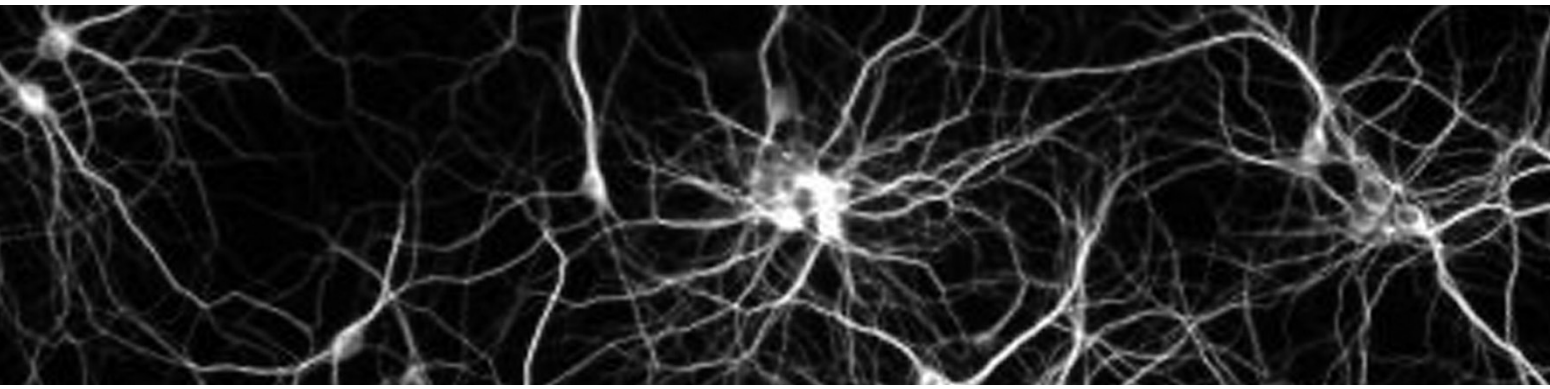

Role of smartphone video in seizure evaluation – our experience

Nevia Novak[1], Frederic-Ivan Silconi[1], Ivana Vidović Vujačić[1]

ABSTRACT - *Objectives*: Epilepsy diagnosis is based on anamnesis given by the patient and people present with them at the time of the seizure. Their description may be inaccurate and delay establishing the correct diagnosis. Availability of smartphones and possibility of creating video recordings at any time provide an important tool to visualize seizure and establish accurate diagnosis. *Case description*: We present three patients from the Epilepsy outpatient clinic in General Hospital Pula, with frequent paroxysmal events, that were initially diagnosed with epileptic seizures and antiepileptic therapy was initiated. Caregivers were advised to record video of paroxysmal events using a smartphone. *Results*: In all three patients, smartphone video proved to be a useful tool in establishing clinical suspicion of psychogenic nonepileptic seizure. *Conclusion*: Smartphone video could be a useful tool in distinguishing epileptic from nonepileptic events (PNES), but are not intended to replace video electroencephalography (EEG), which remains the gold standard in the diagnostic process for PNES.

Keywords: psychogenic nonepileptic seizures, seizure, smartphone, smartphone video

INTRODUCTION

Diagnosis of epilepsy is clinical, i.e., it is based on the patient's history and clinical examination, supported by neuroradiological and neurophysiological assessment. Patient´s history is mainly based on a description of event provided by witnesses. This description could be inaccurate and result in the faulty characterization of a paroxysmal event as epileptic, with the consequent introduction of antiepileptic therapy (AET). Consequently, treatment cost increases and the patient is exposed to adverse effects of AET. Differential diagnoses of seizures are broad and represent a clinical challenge, especially in case of psychogenic nonepileptic seizures (PNES). PNES are paroxysmal episodic events that resemble epileptic seizure and are often misdiagnosed as an epileptic seizure. According to the literature, approximately 20%-40% of patients admitted to the epilepsy monitor unit due to refractory seizures are diagnosed with PNES (1).

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Video EEG is the "gold" standard in establishing definitive diagnosis of PNES, but it is not always available in all hospitals. Smartphones are widely available devices with the possibility of recording high-quality videos of a patient´s seizure and sharing video files with a physician (neurologist/epileptologist), who would analyze it and then use it as an additional tool in distinguishing epileptic events from nonepileptic ones.

MATERIAL AND METHODS

We present case reports of three patients from our outpatient epilepsy clinic (General hospital Pula, period from 2019 to 2021): two male patients (37 years old and 50 years old) and one female patient (34 years old) with frequent paroxysmal events that were initially diagnosed as epileptic seizures. Diagnosis was made according to available anamnestic and heteroanamnestic data and AET was initiated.

Patient 1 (female, 34 years old) has had frequent paroxysmal events for the last ten years, which her mother described as "difficulty waking up", eyelid fluttering, and jerking of both hands. During an awake period, she has had frequent events with loss of consciousness with jerking of both hands and in postictal period she seemed scared. A neurological exam revealed spastic paraparesis. She underwent Pudenz valve implantation in early childhood. First electroencephalography (EEG) was described as pathological (epileptiform changes) and AET (levetiracetam) was initiated. Brain magnetic resonance imaging (MRI) showed Arnold Chiari malformation, corpus callosum dysgenesis, and subependymal nodular gray matter heterotopia. Repeated EEGs were normal, but due to frequent seizures dose of AET was increased with no improvement. Since video EEG monitoring is not available in our hospital, the mother was suggested to record events with a smartphone. After analyzing recorded smartphone videos PNES was suspected. This was later supported by visualization of her event during routine EEG recording in an outpatient epilepsy clinic (no epileptiform activity recorded on EEG during the event) and receiving information about traumatic experiences during childhood (bullying in school).

Patient 2 (male, 37 years old) suffered from frequent jerks of both hands and legs, with olfactory sensations and preserved consciousness. In postictal period he felt tired and exhausted. Brain MRI, EEG, and neurological examination were normal. The seizure was qualified as epileptic according to patient's history and AET (levetiracetam) was initiated, without any improvement in seizure frequency. During recording EEG after sleep deprivation patient's seizure was visualized (jerking of both hands, side-to-side head movements, preserved consciousness, normal speech, opisthotonus) without epileptiform activity on EEG. History revealed traumatic experience during childhood (father was alcoholic and aggressive). PNES was suspected. In the meantime, mother recorded a video using a smartphone: events include asynchronous jerks of both hands and right leg, eye closure, side-to-side head movement, hyperventilation, and carpal spasms.

Patient 3 (male, 50 years old) has been followed for approximately ten years in our outpatient epilepsy clinic due to epilepsy. Brain MR was normal as well as EEG. His history revealed traumatic experience from war. Seizures occurred in different time intervals, despite AET (sodium valproate). According to his wife's description, during a seizure he loses consciousness with jerking, preceded by involuntary movement of left hand. His wife was advised to record video of his events using a smartphone. Recorded smartphone video revealed attacks suspicious for PNES (patient lying on the floor, turning head side to side, asynchronous movements).

RESULTS

All three patients were referred for video EEG monitoring, psychological testing, and psychotherapeutic support. AET was successfully discontinued in the case of a female patient, who was diagnosed with clinically established PNES, and in the case of a younger male patient (35 years old) who performed video EEG, and diagnosis of documented PNES was made. The second male patient (50 years old) is still taking AET, diagnosis of probable PNES was made and he was referred to the Epilepsy center for video EEG.

DISCUSSION

Taking patient's history and physical examination is crucial for the evaluation of paroxysmal events, but often history obtained from witnesses seems inadequate or inaccurate, which can mislead neurologist to diagnose epilepsy. Smartphone video is a useful adjunctive tool in clinical evaluation of seizures, especially in patients with frequent seizures despite AET.

The following recommendations are proposed for quality smartphone video recording of seizures: re-

cord the events from the onset, including ictal and postictal period, duration of video should be 2-3 minutes; maintain interaction with patient (asking simple questions); record the patient's entire body; ensure adequate lightning of surroundings, video recording should not be blurry; most importantly ensure patient's safety (2,3).

CONCLUSION

A combination of smartphone video, patient´s history, and physical examination could be useful in distinguishing epileptic from nonepileptic events (PNES), especially in circumstances when video EEG monitoring unit is not available. Smartphone videos are auxiliary method, not intended to replace video EEG, which remains the gold standard in the diagnostic process for PNES.

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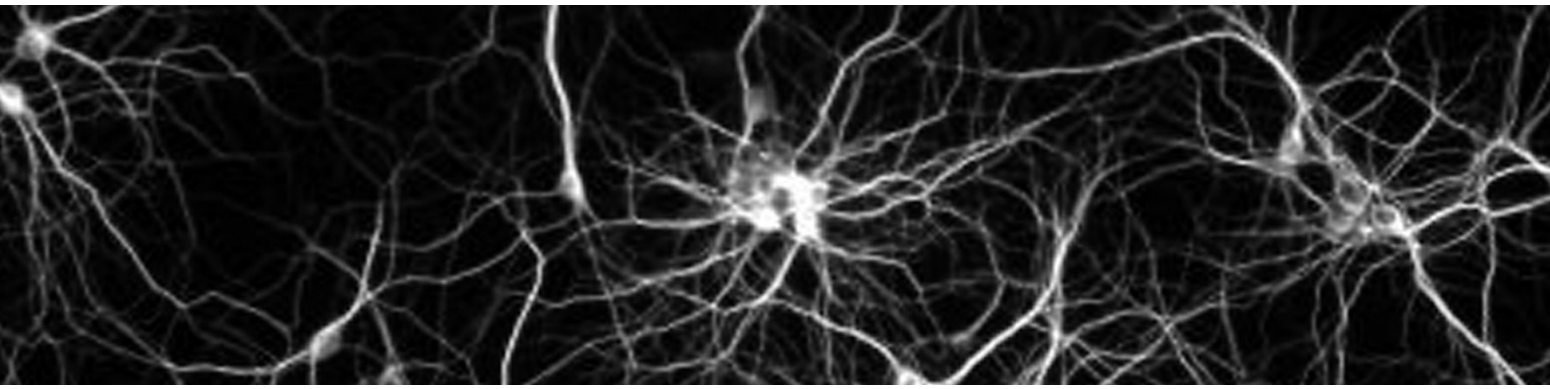

Bilateral thalamic hyperintensities in acute encephalitis: a diagnostic dilemma

Romana Perković[1], Lovro Hrvoić[2], Ivan Đureković[2], Vlatko Šulentić[1], David Ozretić[3], Fran Borovečki[1,2]

ABSTRACT – *Objectives:* A magnetic resonance imaging (MRI) scan of a 65-year-old man presenting to the emergency room with symptoms suspicious for acute encephalitis revealed bilateral thalamic lesions, which, while uncommon, have a broad differential diagnosis. *Case description:* Here we present a male patient with subacute onset of headache, confusion, behavioural changes, cognitive impairment, and fever on two occasions, in 2015 and 2019. *Results:* Several metabolic disorders (anti-MAG associated neuropathy and gangliosidoses), autoimmune disease (autoimmune encephalitis), malignant processes, and infectious causes were excluded from differential diagnosis based on clinical image, computed tomography (CT) and MRI scans, electroencephalography (EEG), and results from polymerase chain reaction (PCR) and serological testing, which leaves a possibility of Japanese Encephalitis Virus (JEV) infection. Our suspicion of JEV infection is further supported by a few reports of similar clinical images and findings in patients with probable JEV infection. *Conclusions:* In encephalitis, brain imaging should always be conducted to keep track of disease progression. Flavivirus encephalitis should be taken into consideration in case of bilateral thalamic hyperintensities on MRI. The patient should be tested for IgM anti-JEV antibodies to either confirm our suspicion or exclude JEV from the differential diagnosis.

Keywords: bilateral thalami, flavivirus, MRI, neuroimaging

OBJECTIVES

We are reporting a clinical case of a currently 68 years old male patient who presented multiple times to the emergency room (ER) in the past decade with symptoms of acute encephalitis and bilateral thalamic lesions visible on diffusion-weighted

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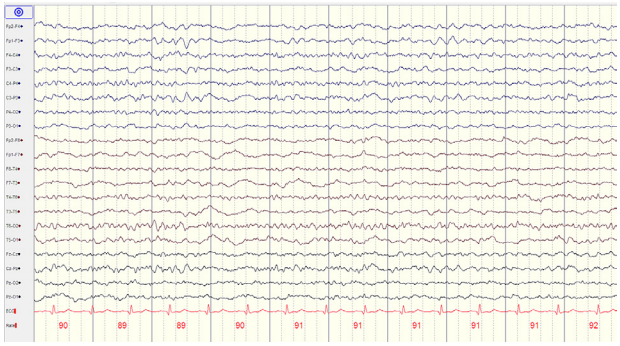

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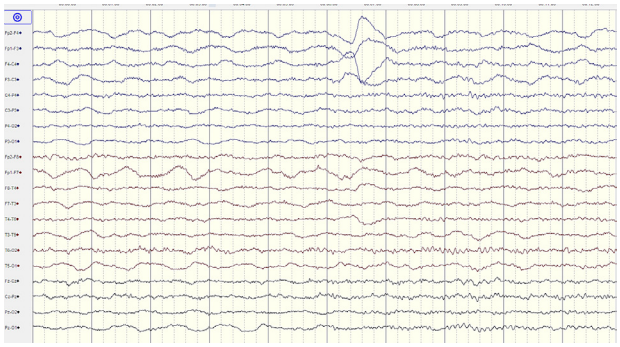

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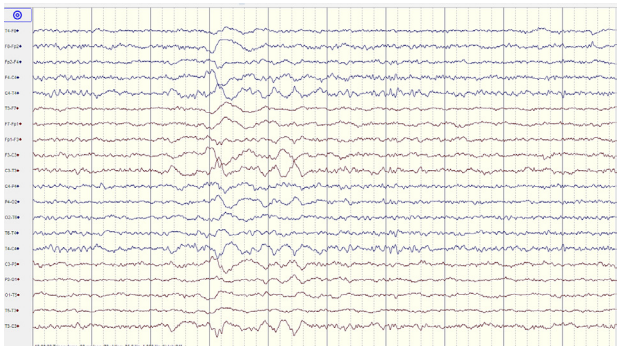

Fig. 1. *EEG recordings made during the patient's second hospitalisation in June 2019 on three separate occasions: (a.) diffusely dysrhytmically changed brain activity with left focal slowing is visible, especially in the left frontotemporal region; (b.) left focal slowing and LRDA in the left hemisphere; (c.) left focal slowing centroparietotemporally with generalized discharges of slow activities and elements of sharp wave activities.*

magnetic resonance imaging (DW-MRI) providing us with an interesting diagnostic conundrum. Bilateral thalamic lesions are not common but can be a manifestation of various metabolic disorders, demyelinating disorders, infection, neoplasm, or vascular occlusion, which all had to be considered in the patient's differential diagnosis (1).

CASE DESCRIPTION

In March 2015, a 61-year-old man presented to the ER describing nausea and a diffuse headache of previously not experienced intensity. The patient's spouse also reported changes in his behaviour and episodes of subacute intermittent confusion dating back a few months. The conducted neurological examination revealed spatial and time disorientation with no other pathology detected. The computed tomography (CT) scan (*Somatom Definition AS, Siemens Healthineers, Germany*) revealed an arachnoid cyst in the posterior cranial fossa, positioned medially, with little to no visible compression on the vermial structures of the cerebellum. Cerebrospinal fluid (CSF) analysis yielded no pathological findings but blood tests showed slightly elevated leukocytes ($12.87x10^9$/L). The patient was admitted to the Department of Neurology at the University Hospital Centre Zagreb. During hospitalization, several chronic lacunar lesions of the basal ganglia and the bilateral deep periventricular white matter were detected on MRI (*Magnetom Aera 1.5T, Siemens Healthineers, Germany*). Diffuse slow waves more prominent in the right frontotemporal region were recorded on the electroencephalogram (EEG) (*Natus 32 canal EEG system Nicolete video EEG, Natus, Ireland*). The patient was diagnosed with ischemic leukoencephalopathy, which was thought to be a satisfactory explanation for the altered mental status component, and was discharged from the hospital in April 2015.

The patient presented to the ER again in June 2019, this time with fever, severe headache, incoherent speech, sensorimotor dysphasia, and right-hand paresis, under the diagnosis of non-convulsive status epilepticus (NCSE). Leukocytosis was detected again ($11x10^9$/L) with slightly elevated polymorphonuclear levels and low lymphocytes, but CSF analysis and CT scan failed to detect any pathology. EEG findings revealed diffuse slowing activity with periodic focal slow wave activity of the left

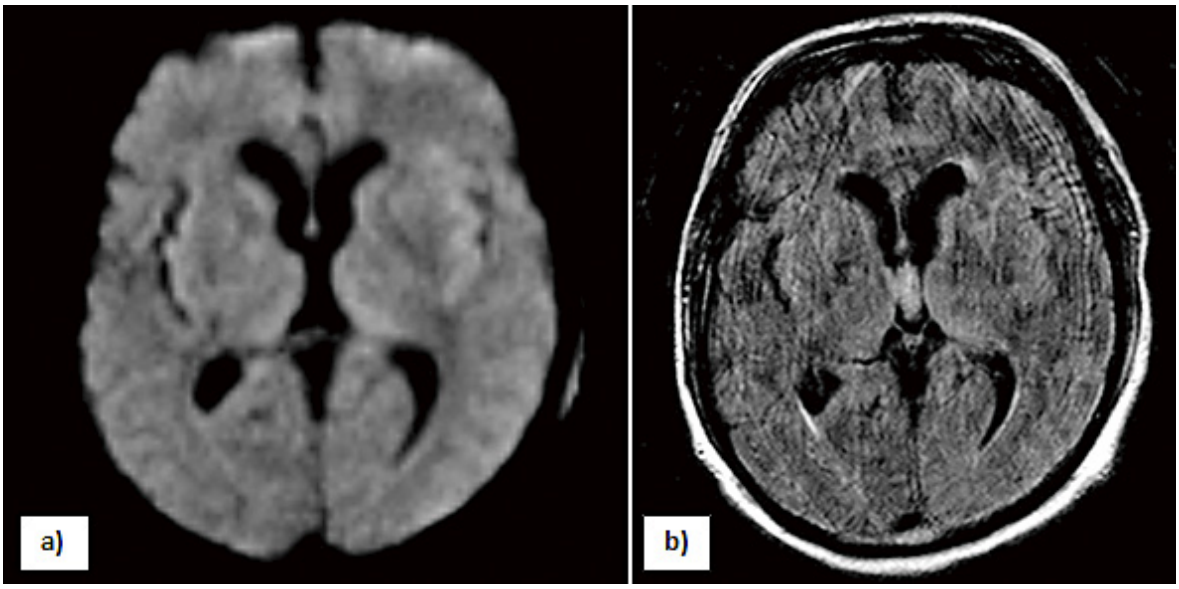

Fig. 2. *MRI hyperintensities in posteromedial thalami and change of signal in the insular cortex on the: (a.) diffusion-weighted imaging (DWI); (b.) fluid-attenuated inversion recovery (FLAIR).*

temporal lobe (Fig. 1a). The patient was hospitalised and MRI was performed which revealed several chronic vascular lesions in the frontoparietal and periventricular deep white matter along with microangiopathic changes of novel origin. On the following day, another EEG was performed which showed lateralized rhythmic delta activity (LRDA) in the left hemisphere (Fig. 1b). The patient remained febrile and confused which prompted the use of intravenous immunoglobulin (IVIG) treatment, as well as levetiracetam, ceftriaxone, acyclovir, and corticosteroids which led to a slight improvement in his clinical status.

MRI diffusion-weighted imaging (DWI) sequence performed a few days later showed hyperintensities in the medial sections of both thalami and the left insular cortex (Fig. 2). EEG showed slow wave activity in the left centrotemporoparietal region with generalized discharges of slow activity with elements of sharp wave (Fig. 1c). IVIG therapy was continued and the patient showed a steady improvement in mental function.

The patient was hospitalised at the Department of Neurology on two more occasions, first in November 2019 and later in June 2020, to receive the 5-day IVIG treatment. Following the last treatment, the patient was reported to be normally functioning.

RESULTS

The patient underwent a plethora of diagnostic procedures to narrow down the differential diagnosis for acute encephalitis and bilateral thalamic lesions. Gangliosidoses, malign diseases, neurotropic viral infections, and autoimmune diseases including acute disseminated encephalomyelitis (ADEM) and autoimmune encephalitis (AIE) were among the diagnoses taken into consideration.

The patient was tested for anti-myelin-associated glycoprotein (anti-MAG) antibody associated with anti-MAG peripheral neuropathy, and several anti-ganglioside antibodies (anti-GM1, anti-GM2, anti-GD1a, anti-GD1b, anti-GQ1d) which were all negative, eliminating suspicion of a metabolic disorder (2). CT scan of thorax, abdomen, and pelvis found no evidence of cancer, and anti-Hu, anti-Ri, and anti-Yo paraneoplastic antibodies were negative, removing malignant cause from differential diagnosis.

Subacute onset of headache, confusion, behavioural changes, impaired cognitive functioning, and fever combined with vascular pathology of the basal ganglia and normal CSF parameters aroused the suspicion of AIE. Still, the patient's AIE panel came back negative. The slow wave, high voltage delta activity coupled with LRDA pattern has also been documented in patients with AIE, but given the criteria for evaluating patients for AIE based on the paper by Graus *et al.*, this diagnosis was excluded as AIE is not likely to present itself with no temporal or limbic pathology along with negative serology (3).

Because of a positive response to IVIG during the second hospitalization, the possibility of acute disseminated encephalomyelitis (ADEM) was also considered (4). Bilateral thalamic lesions have been

previously associated with ADEM, but rarely as the only visible lesion (5). Up to 40% of all patients with ADEM show thalamic involvement, while bilateral lesions have been reported in approximately 12% of the paediatric population (6). In most cases, MRI-DWI shows increased diffusion in ADEM lesions (7). Fever is more frequently described in ADEM than in other demyelinating syndromes and the acute presentation of ADEM encephalopathy can sometimes be preceded by prodromal symptoms such as irritability, nausea, or headache. The clinical course of ADEM progresses rapidly, within 2-5 days, leading to polyfocal neurologic deficits. While our patient's relapse in 2019 resembles ADEM both in symptoms and imaging results, the first episode in 2015 cannot be explained by this diagnosis, because of the lack of characteristic findings on MRI and clinical image which did not progress past the initial headache and confusion despite the absence of corticosteroid or IVIG therapy.

The infectious cause was heavily considered. The combination of fever, leukocytosis (primarily polymorphonuclears), increased C-reactive protein (CRP) and probable NCSE resembles the herpes simplex virus (HSV) encephalitis. While all parameters in our patient's CSF were within normal range which is not usual for an HSV infection, there have been reported cases of HSV encephalitis with no abnormalities in CSF (8). However, HSV-1 and HSV-2 were excluded by a polymerase chain reaction (PCR) test and serological analysis of CSF. Further, PCR and serological testing of blood, urine, and CSF was conducted to exclude Varicella Zoster Virus (VZV), cytomegalovirus (CMV), Epstein Barr Virus (EBV), enteroviruses, West Nile Virus (WNV), *L. monocytogenes*, *M. pneumoniae*, *C. pneumoniae*, *B. burgdorferi, Anaplasma* and *Toxoplasma* infection from differential diagnosis.

Another infectious cause that should be taken into consideration due to the patient's symptoms and MRI findings is the Japanese Encephalitis Virus (JEV). Bilateral thalamic lesions in MRI are most often visible in viral encephalitis caused by the *Flaviviridae* family, namely JEV and WNV (9). In absence of serology, Dung *et al.* demonstrated on a cohort of 75 patients that combined CT and MRI results could be used as a possible diagnostic predictor of JEV with a sensitivity of 23% and specificity of 100%. This MRI pattern, alongside temporal lobe and insular core hyperintensity, has also been observed before in six cases of acute viral encephalitis of suspected JEV and HSV aetiology (10).

Our patient was tested for WNV, but not for JEV. Patients with Japanese Encephalitis exhibit symptoms of headache, fever, convulsions, and altered sensorium which is in line with the clinical image of our patient (11). JEV infection is also often presented with slightly or substantially elevated neutrophils and in some cases CSF pleocytosis. In addition, an EEG pattern of diffuse polymorphic delta activity and delta activity with spike or sharp waves has been recorded in patients with JEV which corresponds to the EEG activity of our patient (12). It is important to note that, although the LRDA pattern is highly sensitive to JEV, it is not specific enough by itself. JEV infection could also explain the relapsing episode of encephalitis in our patient; Japanese Encephalitis has an acute onset in the majority of cases, but chronic infection is possible and it has been previously suggested that it is mediated by chronic persistence of the virus in host's lymphocytes and spleen.

CONCLUSIONS

In encephalitis, brain imaging should be conducted to help differentiate between possible causes as well as keep track of disease progression. Differential diagnosis of bilateral thalamic hyperintensities on MRI should not be approached lightly, and all necessary diagnostic procedures should be taken to narrow down the broad differential diagnosis ranging from metabolic and neoplastic disorders to infectious causes. Among other potential diseases, bilateral thalamic lesions should always raise suspicion of flavivirus encephalitis. We suggest that serological testing for IgM anti–JEV antibodies be conducted to exclude Japanese Encephalitis from differential diagnosis.

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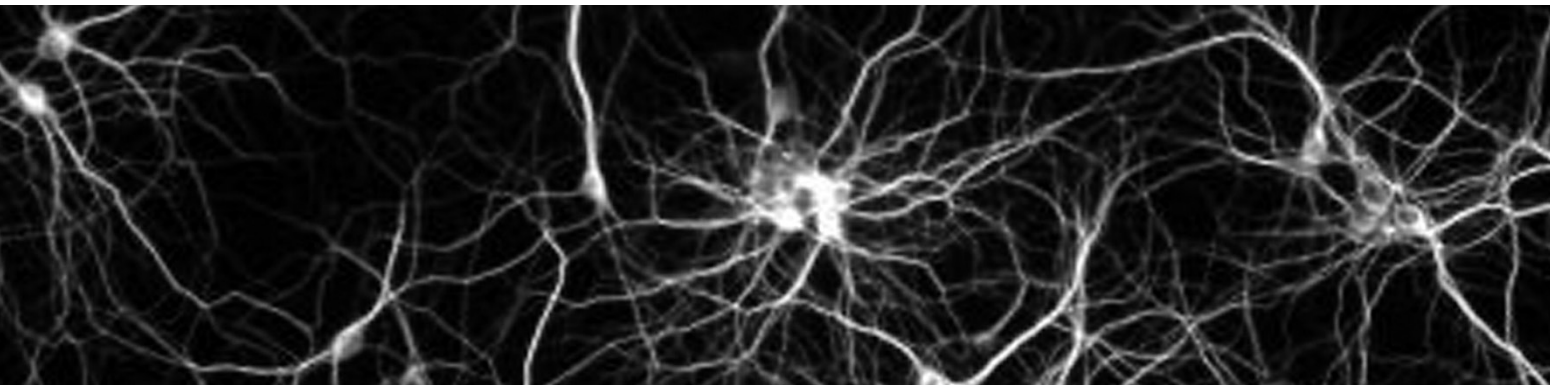

Isolated cranial neuropathy in bilateral internal carotid artery dissection: a case report

Marijana Radić, Vedrana Peček, Frederic-Ivan Silconi, Dolores Janko-Labinac

ABSTRACT - *Objectives*: We present the case of a patient with isolated unilateral glossopharyngeal and hypoglossal nerve palsy and bilateral dissection of internal carotid arteries. Our aim is to remind that carotid artery dissection may present with lower cranial nerve lesion and to discuss therapeutic options. *Case description*: A 48-year-old patient presented with sudden onset of dysphagia, dysphonia, and right-sided facial pain. A neurologic exam also revealed mild pharyngeal weakness and mild weakness of shoulder abduction bilaterally. Brain computed tomography (CT) scan was normal, as well as the initial ear, nose, and throat (ENT) assessment and carotid artery ultrasound. Initial brain magnetic resonance (MR) presented non-specific white matter hyperintensities (WMH) in frontal lobes, while time-of-flight (TOF) MR angiography was interpreted as non-pathognomonic. A week later patient experienced clinical worsening with the appearance of right-sided tongue atrophy. CT angiography revealed right internal carotid artery (ICA) dissection with significant stenosis in petrous segment. Additionally, there was post dissecting aneurysm at C1 segment of left ICA. *Conclusion*: Carotid artery dissection may present with cranial nerve palsy in up to 10% of cases, therefore it should be observed in differential diagnosis of patients with bulbar symptoms. Decisions regarding secondary prevention antithrombotic therapy previously varied between physicians. Based on available studies the 2021 European Stroke Organisation guideline for the management of extracranial and intracranial artery dissection recommends antiplatelet therapy in these cases.

Keywords: carotid artery, internal, dissection, cranial nerve diseases, glossopharyngeal nerve diseases, hypoglossal nerve diseases, anticoagulants

INTRODUCTION

We present the case of a patient with isolated cranial neuropathy and bilateral dissection of internal carotid arteries. A 48-year-old female patient reported to the emergency department due to sudden onset of swallowing discomfort when drinking liquids and voice alteration. The symptoms lasted for two days before visiting the emergency depart-

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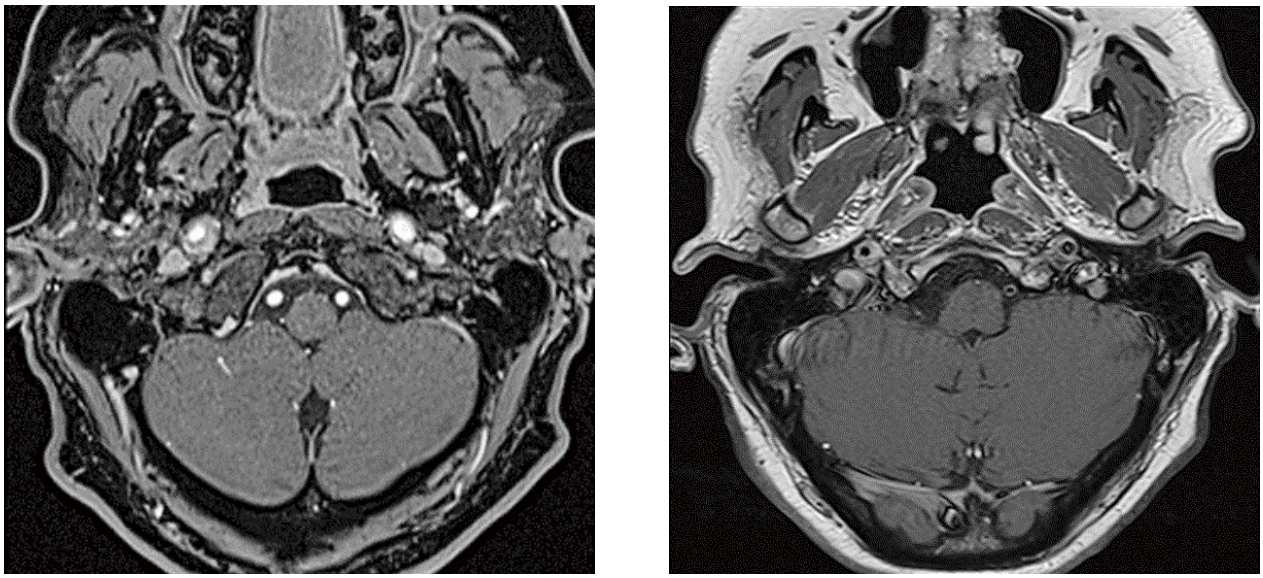

Fig. 1. *Right carotid artery dissection on MRI*

ment and were preceded by pain in the right zygomatic and temporal area.

The patient described mild to moderate non–stabbing pain without visual or hearing impairment. There was no previous trauma or fever. Respiratory infections and earlier tick bites were also excluded. She recounted episodes of increased fatigue during the previous year as well as the occasional sensation of mild eyelid ptosis, without vision disturbances. The patient was a non-smoker, formerly treated for arterial hypertension; therapy was discontinued during the previous year due to normal blood pressure values. A neurological exam revealed hypophonia, mild pharyngeal weakness, and mild weakness of shoulder abduction bilaterally; there was no eyelid ptosis. Emergency work-up included unremarkable laboratory results, negative Neostigmine test, a normal result of brain computed tomography (CT) scan, as well as initial assessment of ear, nose, and throat (ENT) specialist. Upon admission, we performed carotid artery ultrasound which was normal. Magnetic resonance (MR) and TOF MR angiography (MRA) showed nonspecific T2/FLAIR white matter hyperintensities (WMH) in frontal lobes, three in the left hemisphere, and one on the right side, with MRA interpretation of right anterior cerebral artery A1 hypoplasia and lack of presentation of both posterior communicating arteries. Serum and cerebral spinal fluid analysis were unremarkable, except for vitamin D deficiency (23 nmol/L). Complete laboratory results arrived later and ruled out infectious and autoimmune diseases, paraneoplastic syndrome, encephalitis, or myasthenia gravis antibodies.

A week after admission patient experienced clinical worsening with the appearance of right-sided tongue atrophy, tongue deviation to right, more pronounced dysphagia, and dysartrophonia. Further MR analysis (SPACE, T1 vibe FS, T1 Gd) was at first interpreted as normal, but additional consultation with a neuroradiologist pointed to dissection of the right internal carotid artery (ICA) (Fig 1). CT angiography confirmed dissection of the right carotid artery at the turn of the C1 segment with significant stenosis in petrous segment; as well as contralateral small 2 mm pseudoaneurysm at the C1 segment of left ICA, as a result of probable earlier left ICA dissection. Previous medical history did not include any trauma or earlier unilateral symptoms. During the hospital work-up, the patient received low molecular weight heparin and antihypertensives. Upon establishing diagnosis, she was discharged with a recommendation for anticoagulation therapy with dabigatran. Initial improvement of speech and swallowing was observed about three weeks after symptom onset.

At a check-up at three-month interval patient had mild dysphonia and reported occasional mild swallowing difficulties when consuming solids. Follow-up CT angiography performed at that time presented residual nonsignificant stenosis at petrous segment of the right ICA, without changes of left C1 pseudoaneurysm nor new WMH on brain MR. Six months after symptom onset anticoagulation was stopped and switched to anti-platelet therapy with acetylsalicylic acid. The follow-up exam in one year time was normal, the patient remained well and regularly takes antihypertensive medication.

DISCUSSION

Incidence of extracranial artery dissection is estimated to be 2,6–3/100 000 per year, while intracranial artery dissection incidence is even lower in European population (1). Cervicocranial artery dissections occur in 10%-25% of cases of stroke in young and middle-aged adults, carotid artery dissection occurring twice as often compared to vertebral artery dissection. Possible pathophysiologic mechanisms include subintimal tearing as well as intramural rupture of vasa vasorum with dissection between medial and adventitial layer (2). Dissection most often presents with a headache, either as a unilateral headache or focal pain in the head and neck region. In hospital-based series of patients with dissection about two-thirds to three-quarters presented with ischemic stroke or transient ischemic attack or less often retinal or spinal ischemia, with the possibility of bias due to data collection method (3). Ischemic events usually occur several hours to several days following local symptoms (3, 4). US registry of patients with cervical artery dissection who did not experience ischemic event at the time of diagnosis showed that 1,7% suffered an ischemic stroke over the next two weeks. Risk of experiencing a first or recurring ischemic stroke is highest during 14 to 28 days after establishing a diagnosis of cervicocranial artery dissection (4).

Ten percent of patients with ICA dissection present lower cranial nerves palsy (2). There are two suspected pathophysiologic mechanisms: compression of a nerve by subadventitial hematoma or ischemic nerve lesion due to impaired blood supply. Small blood vessels, such as ascendent pharyngeal artery supplying cranial nerves in retropharyngeal region, may be directly affected by dissection at their origin or compressed by hematoma expansion (5). Better availability of neuroimaging techniques improves diagnostic and therapeutic possibilities in patients with cervicocranial artery dissection, with MRI techniques having around 95% sensitivity and 99% specificity (6).

CADISS study explored incidence of ipsilateral ischemic stroke and lethal outcome in patients with extracranial cervical artery dissection receiving antiplatelet or anticoagulant therapy, as well as recanalization rate. During the three-month study period and a prolonged twelve-month monitoring period, there were no differences in outcome between anticoagulant and antiplatelet groups. Recurrent ischemic stroke was observed in 3,2% of participants receiving antiplatelet therapy and 1,6% receiving anticoagulant therapy (6,7).

In 2015 Gensicke *et al.* proposed investigating combined radiological and clinical outcomes in patients with dissection. Patients were observed over 14 days after diagnosing dissection, with a follow-up brain MRI showing new DWI lesions in 23% of participants. Patients with new DWI lesion on follow-up MRI more often initially presented with ischemic event (stroke, transient ischemic attack [TIA]) and occlusion of dissected artery. There were no significant differences in occurrence of new DWI lesions or new ischemic events between groups treated with antiplatelet versus anticoagulant therapy (non-randomized) (8). Radiological and clinical outcomes were also investigated in an open-label randomized study TREAT-CAD, which did not confirm the expected non-inferiority of antiplatelet therapy in the prevention of recurring stroke or lethal outcomes for patients with dissection (9). Patients were treated with acetylsalicylic acid 300 mg or warfarin over three months. Composite outcome of stroke or lethal outcome was observed in 23,1% of participants receiving acetylsalicylic acid (ASA) and 14,6% of patients receiving warfarin. Five of the seven ischemic strokes in the aspirin group occurred (or recurred) on day 1 after treatment onset.

The case described here occurred before the publication of the 2021 European Stroke Organisation (ESO) guideline for the management of extracranial and intracranial artery dissection. Based on available studies Guideline recommends dual antiplatelet therapy to treat patients with symptomatic extracranial artery dissection and symptoms of TIA or minor stroke, with a remark that due to the low incidence of these cases it is unlikely to expect better-powered RCTs (10). In our case decision to treat with anticoagulant therapy was partially induced by a lack of experience and paucity of guidelines at that time.

CONCLUSION

Our aim with the presentation of this case was to remind that ICA dissection should be considered in differential diagnosis of patients with bulbar symptoms. Current literature reports present the highest risk of primary or recurrent ischemic events in the 28-day period following cervical artery dissection, therefore ESO Guidelines recommend treating patients with TIA and minor stroke with dual antiplatelet therapy during a few weeks.

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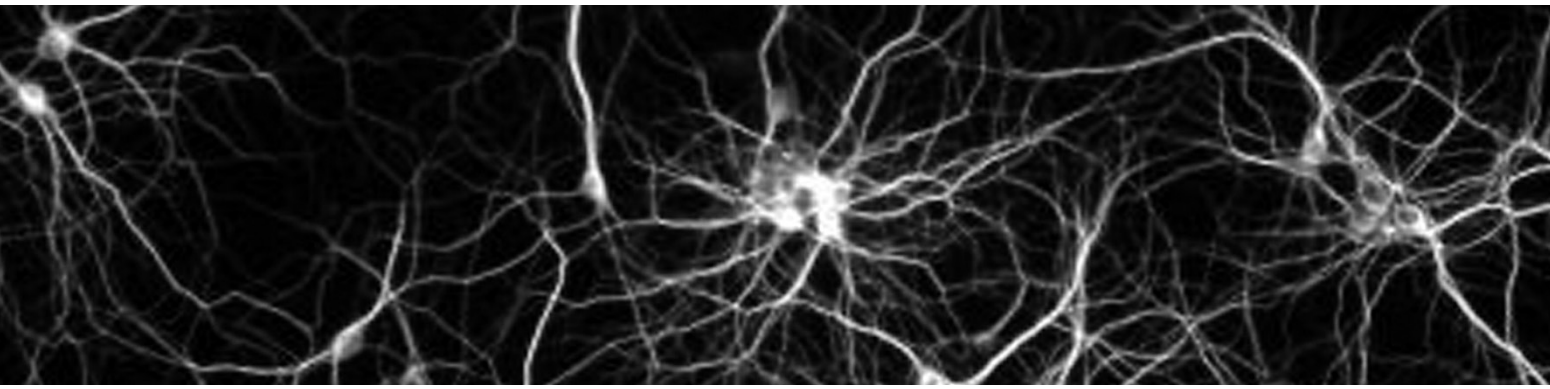

Two cases of artery of Percheron occlusion: odds for a lethal outcome

Frederic-Ivan Silconi[1], Marijana Radić[1], Mihail Poduje[2], Žana Besser Silconi[3]

ABSTRACT – *Objectives:* The artery of Percheron (AOP) occlusion is specific not only by the clinical presentation but also by the outcome. Such infarct involves a small, bilateral, medial part of the thalamus, with or without the rostral part of the midbrain. Because of its anatomic complexity and diversity of nuclei that are involved, we do have such different neurological features. *Case description:* We had two cases of bilateral thalamic infarct due to a variant of the pre-communicating segment (P1) of the posterior cerebral artery (PCA) irrigation occlusion. There have been attempts, through past clinical experience, to determine the most common signs of Percheron artery infarction. These are the three most common features: decreased level of consciousness, cognitive decline or behavioral manifestations, and abnormal eye movement disorders, especially vertical gaze palsy. The first one apparently has a great impact on the outcome and depends on the location and dimensions of the lesion. *Results:* Occlusion of such a minute artery variant was hard to demonstrate. There is no gold standard to demonstrate such an occlusion, but, so far, digital subtraction angiography (DSA) and magnetic resonance imaging (MRI) angiography have more probability to prove such an occlusion. The territorial involvement is best shown by diffusion-weighted imaging DWI MRI, but predicting AOP infarction only by a territorial lesion may be uncertain. Both patients were treated with recombinant tissue plasminogen activator (r-tPA). Our two cases had an opposite outcome, the fatal one we explained by the involvement of the rostral part of the midbrain. *Conclusion:* The AOP occlusion is specific not only by the clinical presentation but also by the outcome. According to our experience, the duration of consciousness deterioration may predict the outcome. Our goal was to emphasize the importance of early detection of AOP infarction.

Keywords: artery of Percheron, bilateral thalamic infarct, impaired consciousness, cognitive impairment.

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INTRODUCTION

The artery of Percheron, (AOP) is an irrigation variant involving the paramedian artery. Usually, the paramedian artery arises from the pre-communicating segment (P1) segment of each posterior cerebral artery (PCA). Occasionally both arteries arise from just one PCA. This variant is present in almost one-third of the population (1). In that case, an occlusion of AOP leads to a bilateral paramedian territory infarct of the thalamus (2). This anatomical variant is schematically explained by the following three figures.

Bilateral thalamic infarcts are rare and according to some stroke series the incidence is estimated at about 0,1%-0,3% of all ischemic strokes (3). Clinical presentation varies, mostly depending on the irrigation variant. There are four more frequent variants, in the following order (3):

1. Bilateral paramedian thalami territory with the rostral midbrain.
2. Bilateral paramedian thalami territory without the rostral midbrain.
3. Bilateral paramedian thalami territory with the rostral midbrain and the anterior thalamus
4. Bilateral paramedian thalami territory with the anterior thalamus and without the rostral midbrain (3).

The first two variants are the most frequent.

CASE REPORTS

We present two cases of bilateral thalamic infarcts, similar in onset characteristics but of opposite outcomes.

Our first patient, B.Z., a 75-year-old male Caucasian with a known history of congestive heart failure, previously determined ejection fraction (EF) of 30%, atrial fibrillation of unknown onset, experienced loss of consciousness while driving. On admission, the patient presented with impaired consciousness and vomiting. Initial exam revealed increased blood pressure (206/134mmHg), he was cardiopulmonary compensated with an arrhythmic action, comatose, Glasgow Coma Score (GCS) 8, pupils were narrow but reactive to light, left-sided hemiparesis with a positive Babinski sign ipsilaterally. The initial National Institutes of Health Stroke Scale (NIHSS) score was 24. During the diagnostic procedure patient temporarily improved to a somnolent state of consciousness with pronounced dysarthria. Initial brain multislice computed tomography (MSCT) did not show signs of cerebral bleeding nor acute ischemia, and MSCTA showed regular branching vessels without large vessel occlusion. He was treated with labetalol for hypertension, followed by administration of recombinant tissue plasminogen activator (r-tPA), Alteplase but stopped at the 18th ml due to unregulated blood pressure and tongue hematoma. During a hospital stay, the patient was treated with therapeutic doses of low molecular weight heparin (LMWH). Different studies support long-term anticoagulation (4). His neurological status deteriorated to cerebral coma complicated with pneumonia. The death occurred on the 14th day of treatment. In this case, we believe that the stroke originated from a cardioembolic source.

Our second patient, P.P., a 69-year-old male Caucasian was admitted due to loss of consciousness. He has a known history of hypertension, diabetes, and chronic lymphocytic leukemia. At admission he was hypertensive, 140/100 mmHg, cardiopulmonary compensated, slightly hyperglycemic, 8,2 mmol/L, and the electrocardiogram showed sinus rhythm. Initial GCS was 3, pupils were narrow but reactive to light. He had right limb hypotonia and a positive Babinski sign on the right side. The patient fully regained consciousness during the radiological workup. Repeated neuro exam showed

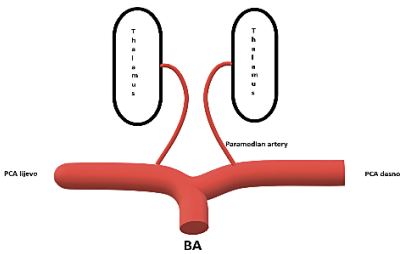

Fig. 1. *Normal irrigation of paramedian territory of the thalami*

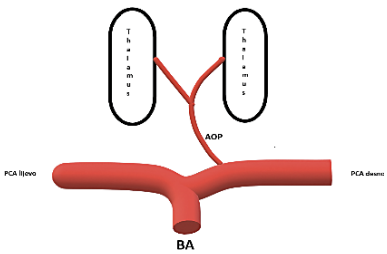

Fig. 2. *Artery of Percheron as a variant*

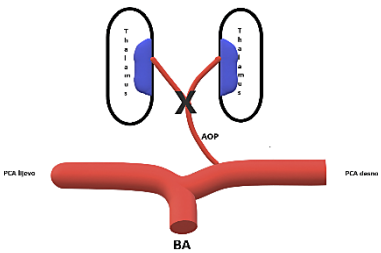

Fig. 3. *Artery of Percheron occlusion and its most frequent irrigation site.*

Illustration by F-I Silconi.

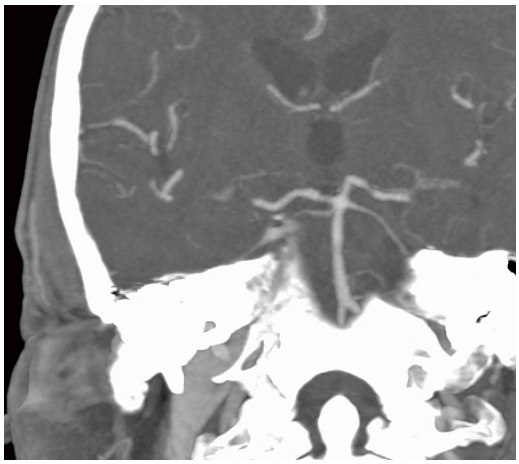

Fig. 4. *B.Z., MSCTA, coronary plane of vertebrobasilar arteries*

aphasia, conjugated gaze deviation to the left, and right-sided hemiparesis, NIHSS 9. NON-contrast brain MSCT was negative, and MSCTA showed normal vessel ramification without large vessel occlusion (LVO). Due to clinical ambiguity, we also performed an MSCTP which differentiated a zone of penumbra in the area of the left middle cerebral artery (MCA). Our patient was treated with r-tPA, Alteplase. He recovered well, the control NIHSS was 6, and macrohematuria was noted. During a hospital stay the pyramidal deficit regressed to a level that he could walk independently with an upper limb paresis accompanied by dysesthesia, but cognitive impairment was pronounced. He was discharged with a single antiplatelet therapy, as suggested in other studies for small vessel occlusion (SVO) (5), even though dual antiplatelet therapy has also been used in similar cases (6). A follow-up after a month showed continuous cognitive impairment, mini-mental state examination (MMSE) 22, with improved motor skills. Heart rhythm monitoring did not detect atrial fibrillation. As large vessel disease was also excluded, we believe that this stroke was a result of an SVO.

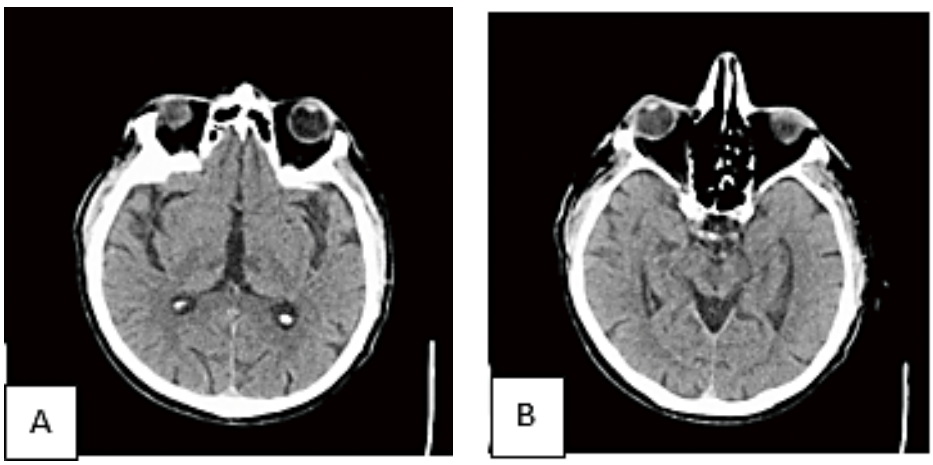

Fig. 5. *B.Z., native axial MSCT, over the thalami region (panel A) and rostral mesencephalon territory (panel B), 24 h after r-tPA treatment.*

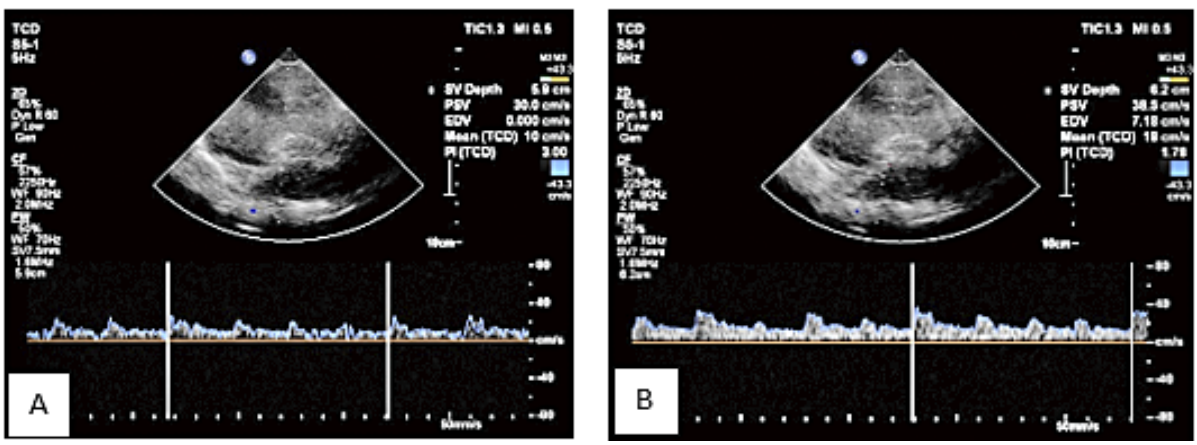

Fig. 6. *B.Z., TCCS posterior circulation: increased vascular resistance on the right P1 segment of PCA (panel A and normal in panel B).*

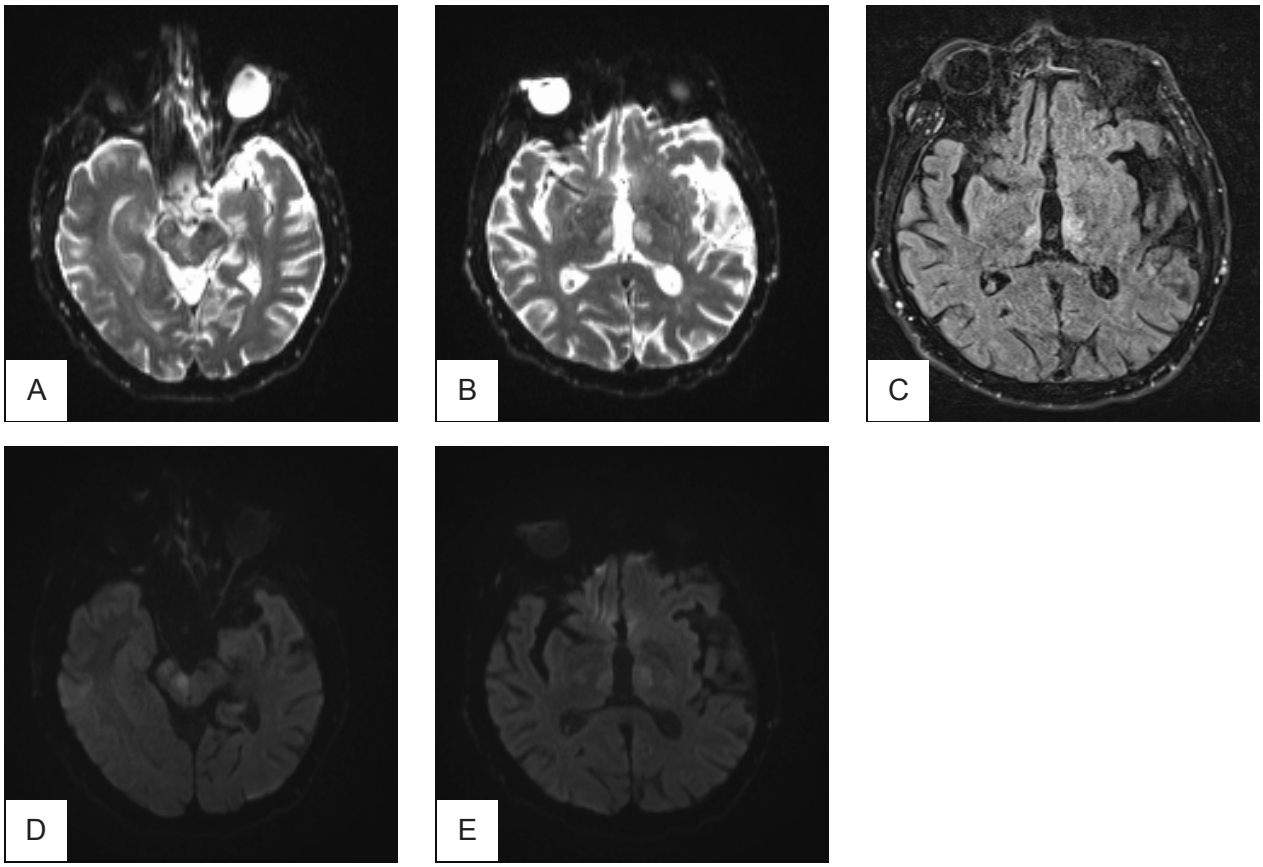

Fig. 7: B.*Z., axial ADC mapping (panel A-B), FLAIR (panel C) and DWI MRI (panel D-E) showing bilateral thalamic ischemia with the involvement of the right cerebral peduncle, on day 11 of onset.*

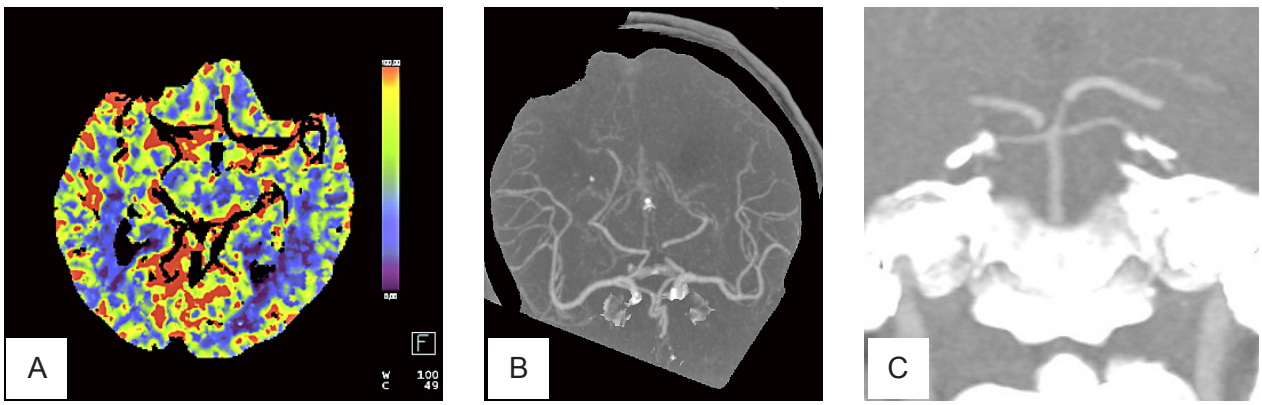

Fig. 8. *P.P., MSCTP (panel A) showing a consistent penumbra on the left MCA. MSCTA (panel B-C), no LVO.*

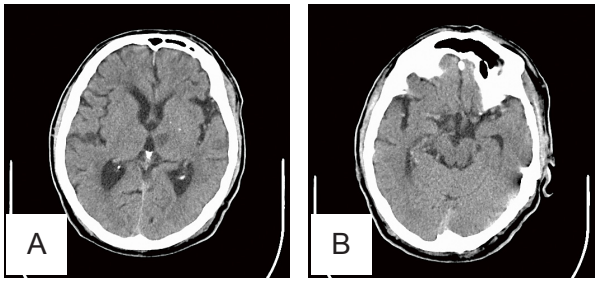

Fig. 9. *P.P., Axial MSCT after 24 h of r-tPA (panel A-B), showing an infarct in the left medial thalami territory. Please note no midbrain involvement.*

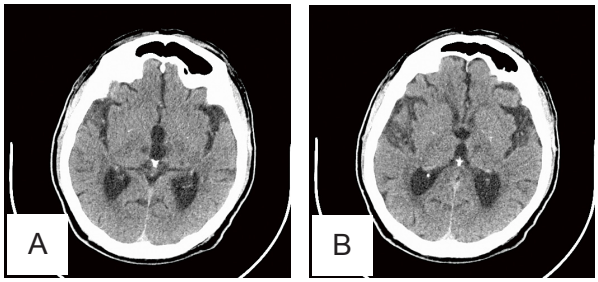

Fig. 10. *P.P., Axial native MSCT (panel A-B), showing bilateral thalamic infarct on day 33 from the stroke.*

DISCUSSION

Lazzaro *et al.* (3) analyzed a large series of AOP infarcts entailing 37 cases. They found a characteristic triad of altered mental status, vertical gaze palsy, and memory impairment. Mental status alterations presented by broad spectrum from drowsiness to coma. The latter was observed in both of our patients, with varied duration. Comma in such patients has been analyzed through a larger number of patients by Tong *et al.* (7). They have differentiated transient and persistent Percheron artery ischemic coma (PAIC), on a sample of 30 and 63 patients, respectively. Researchers found that a higher risk of persistent PAIC was connected to increased NIHSS score at admission and large lesions in the bilateral thalamus and rostral midbrain. By non-adjusted data even AF was more frequent in persistent PAIC. Persistent PAIC patients more frequently had new ischemic lesions on repeated imaging (7) suggesting that the source might be embolic.

Interestingly, both of our patients did not show vertical gaze palsy even though at the first there was a midbrain territory involvement. Presumably, the reason might be due to the disruption of a pathway between the cortex and the medial longitudinal fasciculus (3,8).

CONCLUSION

An AOP infarct often produces focal non-specific symptoms: impaired consciousness, cognitive decline, and gaze palsy (3). We noticed that the length of loss of consciousness depended on lesion location and size. In such clinical cases, urgent magnetic resonance imaging (MRI) should be requested in case of a normal MSCT/MSCTA finding (2,4,8,9,10). The successful outcome of thrombolysis after MRI detecting bilateral thalami infarction has been reported (2,4,6,9,10).

A predictor of a bad outcome is a persistent PAIC, which is dependent on the size of the ischemic lesion measured by the MRI and the severity of clinical presentation measured by available scores (e.g., NIHSS) (7).

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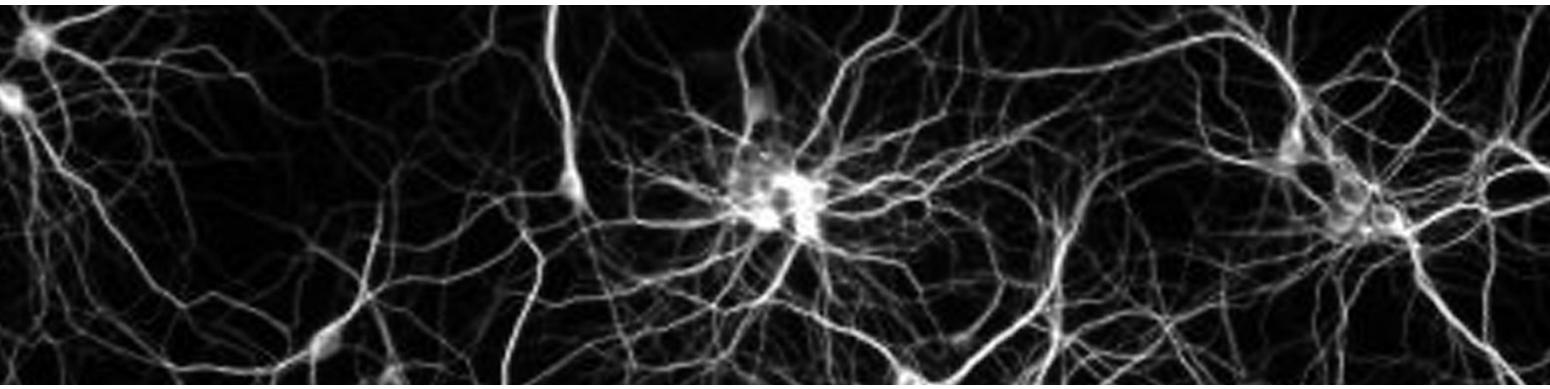

A novel mutation in POLG gene in a patient with progressive external ophthalmoplegia with associated parkinsonism

Mario Špoljarić[1], Stjepan Jurić[2], Romana Perković[3], Zdravka Krivdić Dupan[1,4], Darija Šnajder Mujkić[1,5], Svetlana Tomić[1,2]

ABSTRACT – *Objectives:* The main objective of this case report is a presentation of a novel mutation on both POLG genes in a 50-year-old female patient diagnosed as progressive external ophthalmoplegia with associated parkinsonism. *Case description:* The patient presented with gate instability accompanied by frequent falls, double vision, depression, insomnia, and epilepsy. Neurological status revealed severe parkinsonism with impairment in ocular movements. An extensive diagnostic work-up was performed, and the patient was treated with levodopa and rasagiline that results with only partial treatment response. A sample of EDTA blood was taken from the patient and sent for whole exome sequencing. *Results:* The test results showed two likely pathogenic variants identified in POLG gene, variant c. 752 C > T, and c. 1760 C > T, both heterozygous. *Conclusion:* Patient clinical presentation corresponds to progressive external ophthalmoplegia with associated parkinsonism. Novel mutations in POLG gene, variant c. 752 C > T, and c. 1760 C > T, that was detected in our patient, should be taken into consideration as pathogenic one that can cause this condition.

Keywords: mitochondrial disease, parkinsonism, POLG, progressive external ophthalmoplegia

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INTRODUCTION

The POLG gene is responsible for encoding mitochondrial deoxyribonucleic acid (DNA) polymerase which is important in mitochondrial genome replication (1). The only known DNA polymerase that is capable of maintaining and replicating the genetic material in humans is the DNA polymerase gamma (2). The holoenzyme of the human polymerase gamma has a catalytic subunit which is encoded at chromosomal locus 15q25 by the POLG, and also has homodimeric form of accessory subunit which is encoded at chromosomal locus 17q24.1 by the POLG2. The most likely disease pathophysiology mechanism arises from heterodimerization or haplotype insufficiency of the mutated and wild-type proteins. These mutated proteins promote mitochondrial DNA deletions by interruption of the DNA replication fork. The clinical phenotype is a result of cytochrome C oxidase deficiency that is produced by a progressive accumulation of mitochondrial DNA deletions (3). POLG gene mutations can cause mitochondrial DNA depletion syndromes in early childhood, or they can present as later-onset syndromes. There are several leading disorders caused by POLG mutations which include: Alpers-Huttenlocher syndrome, myocerebrohepatopathy spectrum, autosomal recessive progressive external ophthalmoplegia, myoclonic epilepsy myopathy sensory ataxia syndrome (MEMSA), and autosomal dominant progressive external ophthalmoplegia (4). Alpers-Huttenlocher syndrome is characterized by the early onset of various symptoms which include liver failure and seizures (5). Myocerebrohepatopathy is less common than the Alpers-Huttenlocher syndrome, and it often occurs in infants. It is presented with liver failure, lactic acidosis, and encephalopathy with seizures or without them (6). Myoclonic epilepsy myopathy sensory ataxia syndrome (MEMSA) is a genetic disorder caused by the POLG gene mutation located on chromosome 15. Symptoms of MEMSA first include cerebellar ataxia, later accompanied by epilepsy, encephalopathy, and myopathy. MEMSA syndrome usually affects younger patients (7). Progressive external ophthalmoplegia (PEO) is a progressive condition that is characterized by the involvement of extraocular muscles, resulting in ocular palsy. It can also be accompanied by all sorts of non-ophthalmic manifestations like parkinsonism, hearing loss, depression, ataxia, bulbar myopathy, cardiac myopathy, neuropathy, seizures, or encephalopathy (8). The aim of this paper was to report a novel mutation in both POLG genes in patient with PEO with associated parkinsonism.

CASE PRESENTATION

A 50-year-old right-handed Caucasian female patient was admitted to the neurology department because of gate instability and frequent falls that started one year ago. She complained of double vision, severe vision loss, becoming sluggish, speaking slowly and her handwriting has become small and less legible. Swallowing was preserved but sometimes had saliva drooling. She became increasingly forgetful and has been treated for depression for many years. Sleep was disturbed by severe insomnia and rapid eye movement behavior disorder (RBD). Symptoms of orthostatic hypotension were also reported. In neurological status, severe parkinsonism (symmetrical bradykinesia, hypokinesia, hypomimia, bradylalia with slight dysarthria, severely unstable gate with short steps) was noticed with impairment in ocular movements (staring look, smooth pursuits were saccadic in horizontal plane, vertical movements were limited downwards with only minimal movement to upwards position, saccadic movements were severely impaired in vertical plane, while in horizontal plane she performed them with prolonged latency and hypometrically). She reported double vision in all directions of eye

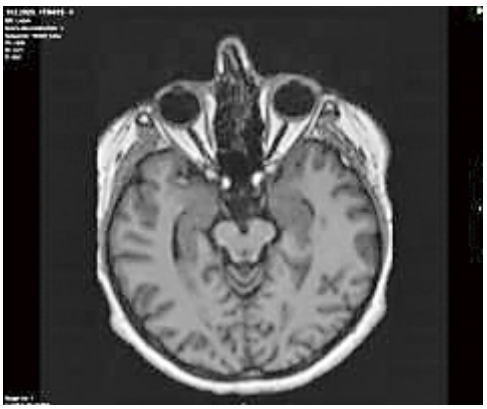

Fig. 1. *MRI transversal T1w image*

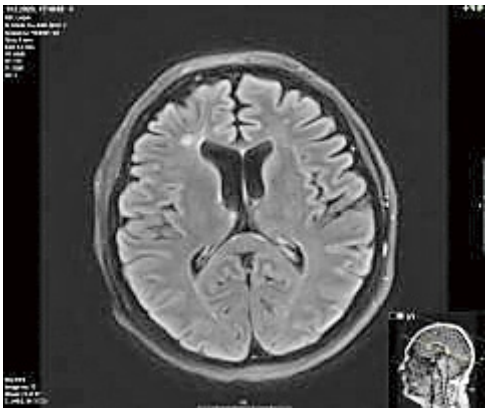

Fig. 2. *MRI FLAIR transverse image*

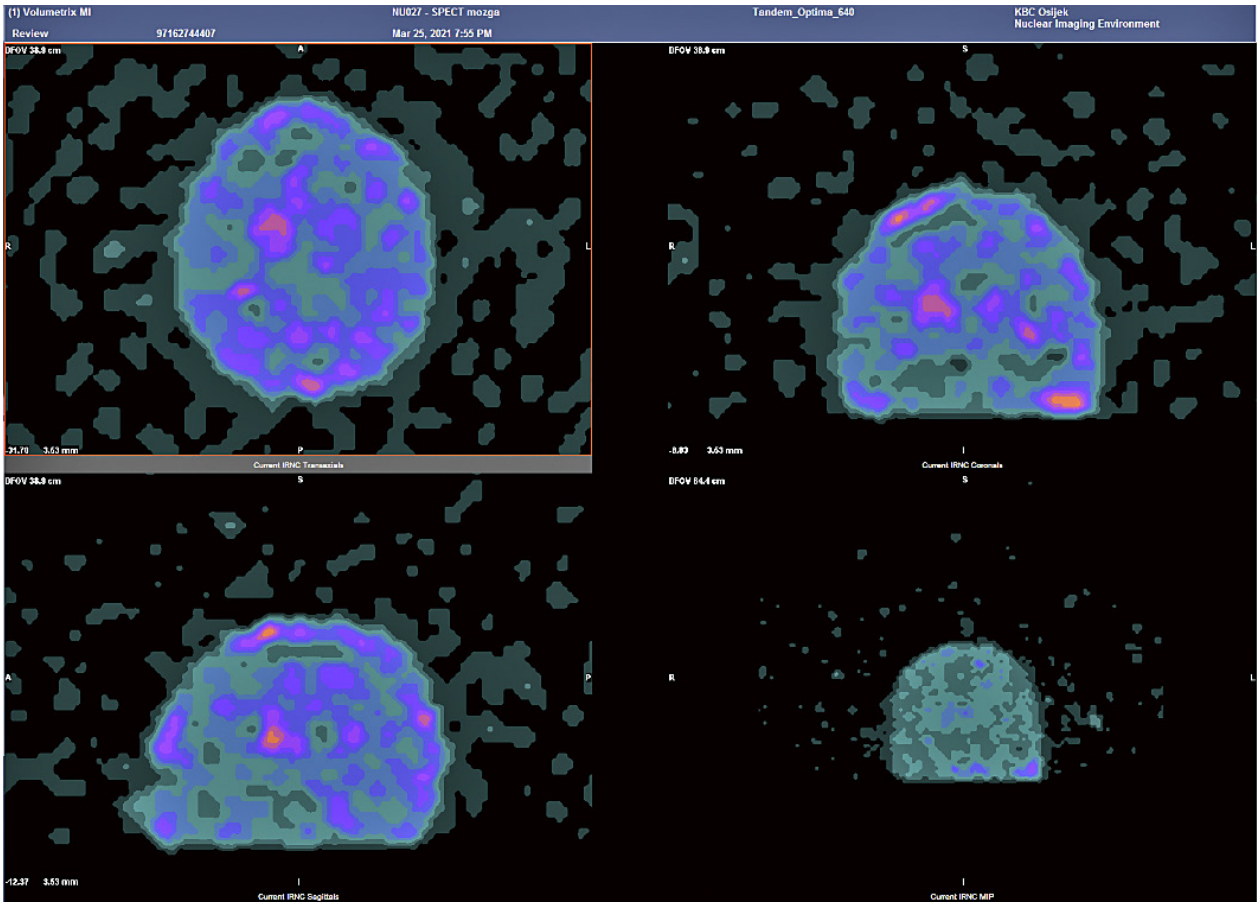

Fig. 3. *DAT SPECT*

movements. No signs of pyramidal tract and sensory system impairment. In her medical history, she suffered from epilepsy since infancy (focal seizure with impaired awareness and atonia). At the age of 49, she has been operated for subcapsular cataract on the left eye. In her family history, there were no patients with movement disorders. The patient underwent extensive diagnostic workup. Magnetic resonance imaging (MRI) of the brain showed, on transversal T1w, an abnormal bright internal signal in extraocular muscles and atrophy (Fig. 1) and on fluid-attenuated inversion recovery (FLAIR) transverse image frontal periventricular white matter hyperintensities (Fig. 2).

Dopamine transporter single-photon emission computed tomography (DAT- SPECT) showed a bilateral deficit (DAT grade II-III on the right side and grade III on the left side) in nigrostriatal system (Fig. 3). She had mild cognitive impairment in multiple cognitive domain (mnestic functions, attention, expressive speech and visuoconstructive abilities). There was no polyneuropathy detected with electroneurography. Genetic testing for Gaucher's, Huntington's, Wilson's, and Niemann Pick's type C diseases were negative. Other diagnostic work-up were normal: cooper in serum and urine, ceruloplasmin, biochemistry (except increased lipid level), anti Hu, Yo, Ri, anti Ma2 antibodies, organic acids, total carnitine, acyl-carnitine profile, mucopolysaccharides in 24-unit urine and oligosaccharides in urine. Levodopa and rasagiline were induced in therapy with only partial response. Genetic testing (whole exome sequencing) was performed after discharge from the hospital. The test was performed in Korean laboratory 3billion using Illumina NovaSeq6000 with IDT xGen kit that is using DNA-based probes for capturing the exome of approximately 35 Mb in size. The sample for testing was EDTA blood. The test results showed two likely pathogenic variants identified in POLG gene, variant c. 752 C > T, and c. 1760 C > T, both heterozygous. The diagnosis of progressive external ophthalmoplegia with associated parkinsonism was made. During the follow-up, her symptoms progress and she became independently immobile.

DISCUSSION

In this paper, we have presented patient with symptoms consistent with a diagnosis of PEO with as-

sociated parkinsonism and whole-exome sequencing (WES) detected novel mutation in both POLG gene. A type of genetic disorder known as mitochondrial DNA depletion syndrome (MDSs) is a group of disorders characterized by mutations in nuclear-encoded genes (9). Slow-progressing bilateral ptosis accompanied by ophthalmoparesis is a common clinical feature of PEO (10). Patients with PEO are also impaired in terms of global cognition and the most affected cognitive areas are language and executive functions. Cognitive impairment could be a consequence of accumulation of mutant mitochondrial DNA in the area of the frontal lobe, which could possibly lead to excessive oxidative stress that affects the function of glial cells and neurons in the frontal lobe (11). Other common clinical features in PEO include symptoms like exercise intolerance and additional symptoms that include eye cataract, ataxia, hearing loss, depression, parkinsonism, hypogonadism, and sensory axonal neuropathy. Often reported dysphagia can be caused by the involvement of peripheral nerves, the central nervous system, or smooth muscles (12). Epilepsy is a common feature of POLG-related diseases. Approximately 50% of patients have epilepsy, presented with focal myoclonic or clonic seizures most often located in the arm, shoulder, or head and neck area. Seizures frequently evolve into focal or generalized status epilepticus. Seizures in both, juvenile and late-onset disease, can be accompanied by vomiting and headache, symptoms that are similar to migraine with aura (13). There have been several cases describing POLG1 mutations with associated parkinsonism, very often secondary to progressive external ophthalmoplegia or ataxia, characterized by late age onset and partial or complete response to L-Dopa (14). Around 200 variants of POLG mutations have been reported that can cause disease, and they can be inherited either by autosomal recessive or autosomal dominant way. Genotype and phenotype correlation of these mutations is not always easy to predict, but there are some exceptions that involve the most common linker region variants (15). Linker region c.1399 G > A is associated with Alpers syndrome that occurs in childhood (16). Recessive ataxia is in correlation with c.2243 G > C, and autosomal recessive PEO is in correlation with c.1760 C > T, which is often located with c.752 C > T on the same allele (17, 18). There are several case reports of PEO with parkinsonism reported novel mutations in the POLG gene, typically c.830 A > T, and c.2827 C > T.19 A case report of a Chinese female patient with optic atrophy, external ophthalmoplegia, and levodopa responsive parkinsonism, reported heterozygote mutations c.2993 C > T, and c.2693 T > C.20 Heterozygous c.2864 A > G mutation was found in two sisters, one of whom had progressive external ophthalmoplegia and developed levodopa responsive parkinsonism at the age of 60, and the other had parkinsonism, polyneuropathy, and PEO (21). In a recent study, an MRI of 20 patients with POLG mutations showed global atrophy, mainly in hemispheric cortex, the amygdala, the basal ganglia, and also in the posterior portion of the brain stem. (22). In a 2016 study, DAT SPECT was performed on 23 individuals with mitochondrial disease. Patients with POLG mutation had striatal denervation that had a faster rate of nigrostriatal degeneration, and the process was progressing symmetrically, unlike in patients with Parkinson`s disease. It is worth mentioning that none of the patients with POLG mutations and nigrostriatal degeneration developed clinical parkinsonism in this study (23). Mutation detected in our patient is in correlation with phenotypic features of progressive external ophthalmoplegia. In addition to ophthalmoparesis, she had a variety of other symptoms including cognitive impairment, eye cataract, epilepsy, depression, and young onset parkinsonism. Genotypically patient had c. 752 C > T, and c. 1760 C > T linker region variant mutations. According to this, we had diagnosed the patient as PEO with associated parkinsonism, which was caused by a novel mutation on both POLG genes.

CONCLUSION

In this case report, we present a patient that had a typical clinical presentation of PEO with associated parkinsonism caused by a novel mutation on the POLG gene. Mutations c. 752 C > T, and c. 1760 C > T should be taken into consideration as one of the many that can cause this condition.

Acknowledgement

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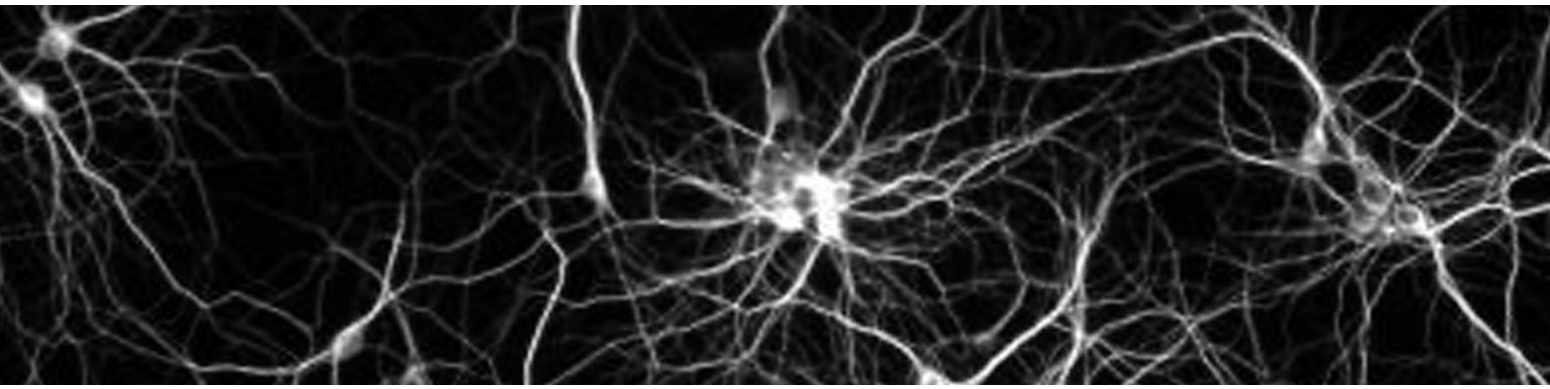

Safety of repeated reperfusion therapy in early recurrent stroke

Svjetlana Šupe[1], Nikola Blažević[1], Zdravka Poljaković-Skurić[1], David Ozretić[1], Josip Ljevak[1], Ivan Perić[1]

ABSTRACT - Thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA) for acute ischemic stroke (AIS) is well-established stroke treatment for almost three decades such as mechanical thrombectomy (MT) in the last 10 years. Current guidelines for thrombolytic treatment of AIS cited a history of a previous stroke within 3 months as a contraindication to re-thrombolytic treatment, which has not been changed since the beginning of the use of r-tPA for AIS treatment.

These recommendations are based on assumed complications with increased risk of symptomatic intracerebral hemorrhage, hypersensitivity reactions, neurotoxic effect, and blood-brain barrier disruption, associated with re-administration of r-tPA in early recurrent stroke with a consequent poor functional outcome. The risk of AIS recurrence within 3 months is about 14%-18%, which strictly based on these guidelines, excludes a large number of patients who suffered a stroke recurrence for repeated intravenous thrombolysis (RIVT), regardless of the needs or possibility for MT.

In recent years, some large case series and case reports have confirmed the safe and effective use of RIVT in early recurrent AIS (ERAIS), without a significant increase in bleeding risk or poorer clinical outcome, indicating the need to amend the guidelines for thrombolytic treatment of recurrent stroke.

We present the case of a patient with ERAIS within 53 hours in whom we conducted RIVT in combination with repeated mechanical thrombectomy with satisfactory functional recovery.

Keywords: stroke, repeated thrombolysis, recombinant tissue plasminogen activator

INTRODUCTION

Treatment of acute ischemic stroke (AIS) using recombinant tissue plasminogen activator (r-tPA) has been established for nearly 30 years and intra-

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venous thrombolysis (IVT) within 4.5 h of AIS onset remains standard management worldwide (1).

The pharmacokinetic properties of r-tPA are known, such as rapid elimination from plasma after administration (50% within 5 min.) as well as side effects with an increased risk of bleeding, especially intracranial haemorrhage, angioedema, reperfusion injury (2,3).

In addition, r-tPA is known to have many, even opposite effects besides thrombolysis. Potentially harmful effects would include excitotoxic neuronal degeneration, damage of the blood-brain barrier (BBB) with increased BBB permeability and inflammation, while potentially neuroprotective effects could be attributed to anti-excitotoxic neurotropic, and anti-apoptotic effects on neurons (4,5).

Despite its effective and relatively safe therapeutic effect, r-tPA is still insufficiently used in the treatment of AIS for a number of reasons, including contraindications for intravenous thrombolysis (6). Current recommendations and guidelines for AIS treatment with IVT highlights recurrent stroke within 3 months as a contraindication to thrombolytic treatment due to the presumed increased risk of symptomatic intracerebral hemorrhage (sICH) and have not changed over the years (7,8).

Early recurrent AIS (ERAIS) represents almost 14.5%-18.3% of all ischemic strokes with the greatest risk during the first week and is considered to contribute to an increased risk of sICH, death, and a poorer functional outcome (9,10,11). Therefore, the possibility of reperfusion treatment with IVT is excluded for a large number of patients with ERAIS (within 3 months), except properly selected patients with proximal occlusions of the large intracranial arteries, suitable for mechanical thrombectomy (12,13,14).

Data from some large case series and case reports published last few years confirmed the safe and effective repeated application of IVT (RIVT) in ERAIS, without a significant increase of IVT-related complications or worse outcomes (15,16, 17).

We present the case of a patient with ERAIS within 53 hours in whom we have successfully conducted RIVT in combination with repeated mechanical thrombectomy with good clinical recovery. We also wanted to emphasize the importance of telemedicine consultation with the designated comprehensive stroke center (CSC) "stroke team" and incorporation of multimodal neuroimaging modalities in assessing the possibilities for repeat IVT and thrombectomy for safe and effective reperfusion treatment in ERAIS.

CASE PRESENTATION

Our patient is a 54-year-old man with a history of hypertension and alcoholism presenting to a regional hospital emergency room with severe right-sided hemiparesis, dysarthria, bilateral VI-th nerve palsy, and right facial palsy, National Institutes of Health Stroke Scale (NIHSS) of 12, premorbidly the patient was without disability (mRS 0). Initial workup, computer tomography (CT), and CT angiography (CTA) showed basilar artery occlusion (BAO) and right vertebral artery dissection and occlusion (Fig. 1). Intravenous thrombolysis was started and after telemedicine consultation with our stroke team the patient was transferred to our comprehensive stroke center (CSC).

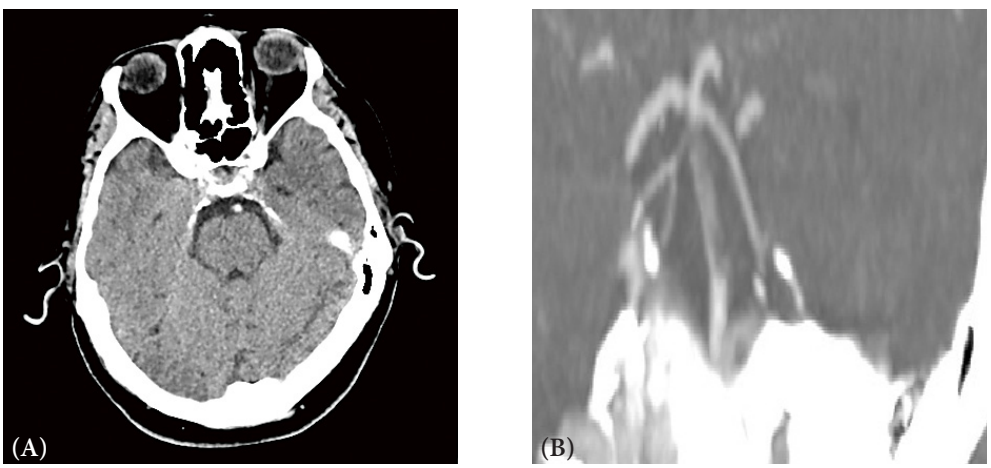

Fig. 1. *Native CT (A) of the brain and CT angiography. (B) during initial workup in the regional hospital showing BAO.*

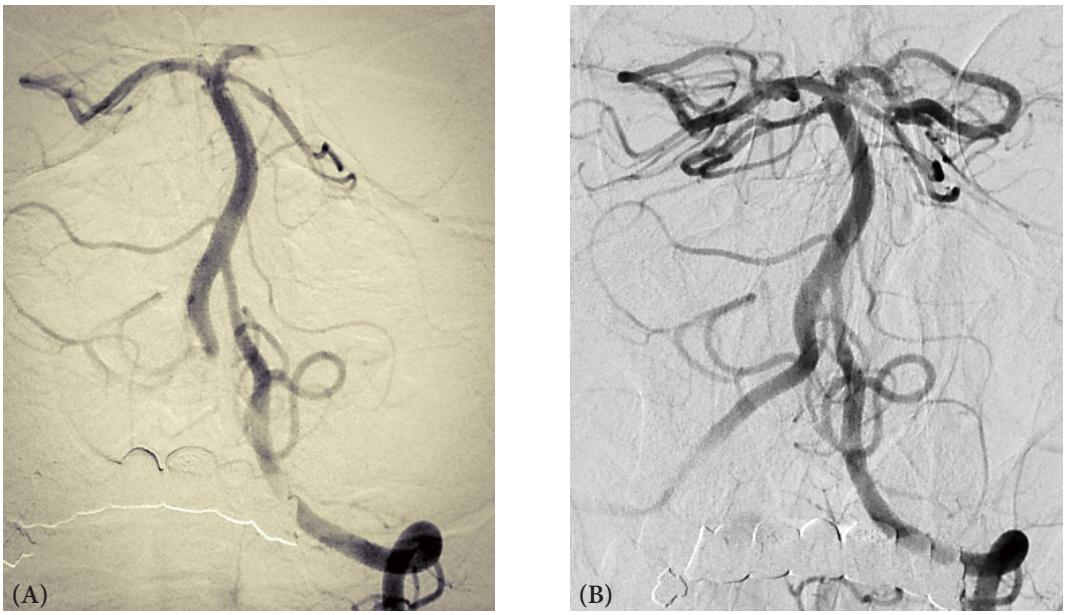

Fig. 2. *(A) – The first angiography showed recanalisation of the basilar artery with occlusion of the right upper cerebellar artery and partial occlusion of the left upper cerebellar artery. (B) - Complete recanalisation with manual aspiration and using a stent retriever.*

Upon arrival at our CSC neuro-intensive care unit (NICU) the patient had mild right-sided weakness, dysarthria, right facial palsy, and bilateral abducens palsy – NIHSS 5, his blood pressure was 170/90 mmHg, heart rate 57. In the angio suite, the patient vomited after which he received antiemetics and a nasogastric tube was placed. The first angiography showed recanalisation of the basilar artery with occlusion of the right upper cerebellar artery and partial occlusion of the left upper cerebellar artery (Fig. 2A). Full recanalisation was achieved (Fig. 2B). Control CT showed small ischemia of the left mesencephalon and left cerebellar cortex (Fig. 3), so we began giving a therapeutic dose of low molecular weight heparin (LMWH). On discharge and transfer from our CSC to the regional hospital the patient had dysarthria, right facial palsy, and right abducens palsy – NIHSS 3.

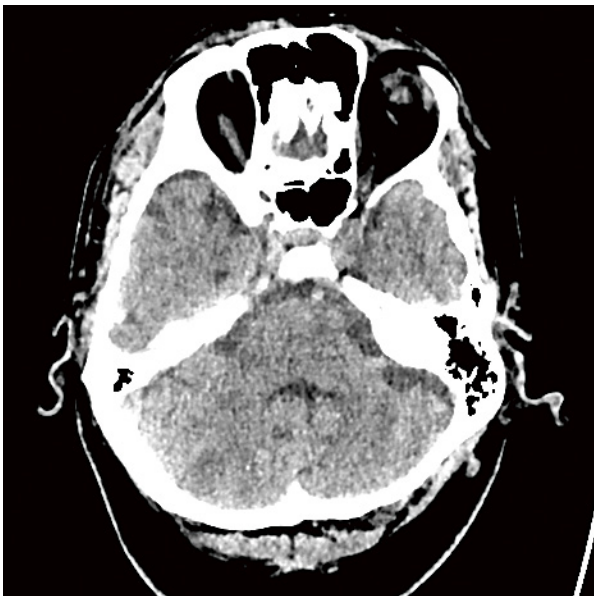

Fig. 3. *Control CT showed small ischemia of the left mesencephalon and left cerebellar cortex.*

We received another telemedicine consultation from the regional hospital regarding the same patient 53 hours after discharge. This time the patient presented with impairment of consciousness with a Glasgow Coma Score (GCS) of 5, involuntary movements of the right extremities, and with a surge of systolic blood pressure above 200 mmHg, he was treated with diazepam and urapidil and was intubated for airway protection. Workup showed reocclusion of the basilar artery with formerly described ischemia (Fig. 4).

Considering the severity of the clinical presentation of the new infarct, favorable outcome with only minimal ischemic changes on the control CT done at our institution we advised repeated intravenous thrombolysis (RIVT) which was administrated 53 hours from the first application and subsequently the patient was transferred to our CSC for another thrombectomy. Upon arrival, the patient was sedated and intubated with small reactive pupils.

In the angio suite angiography showed residual thrombus in the lumen of the middle third of the

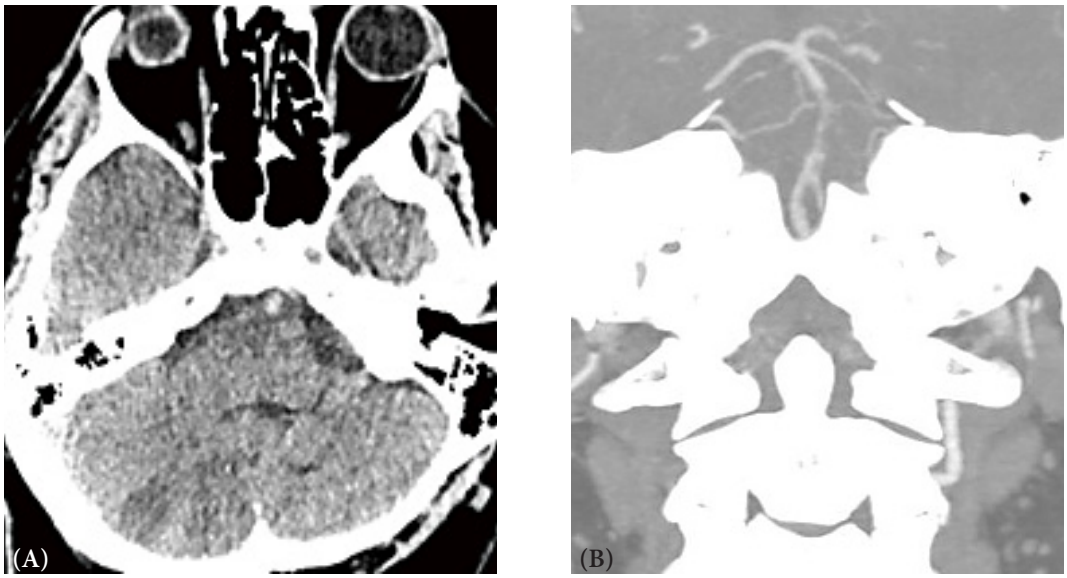

Fig.4. *Control native CT (A) and CT angiography (B) showing reocclusion of the basilar artery and with ischemia of the cerebellum and mesencephalon.*

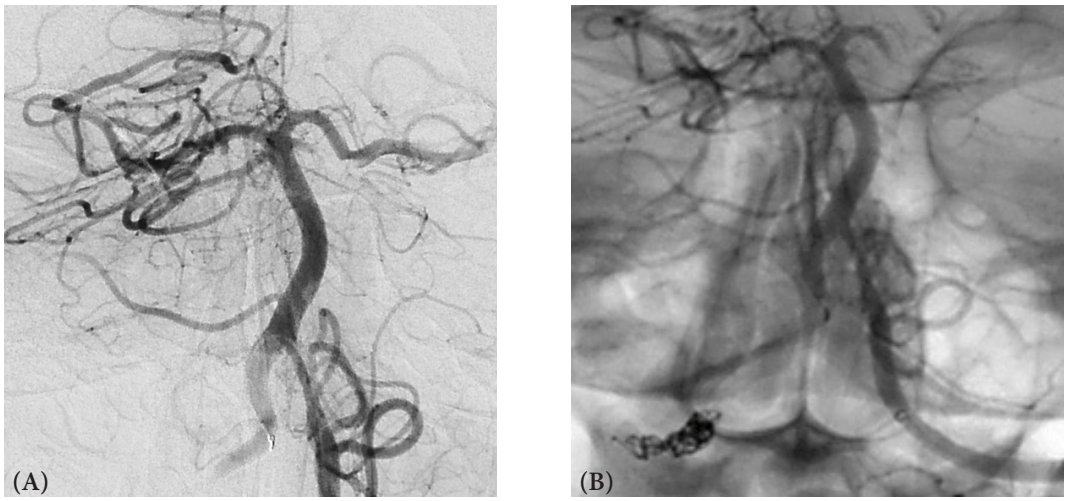

Fig. 5. *(A) angiography showed partial recanalisation of the basilar artery with a residual thrombus in the middle third of the basilar artery and occlusion of the left superior cerebellar artery. (B) Occlusion of the dissected right vertebral artery using five endovascular coils.*

basilar artery, occlusion of the left superior cerebellar artery, and left posterior inferior cerebellar artery (Fig. 5A) which were aspirated with complete recanalization during the endovascular procedure. Right dissected artery was identified as the source of the new emboli, as a preventive measure, we occluded the artery using 5 endovascular coils (Fig. 5B).

Control MRI showed acute ischemia of the left and right cerebellar hemisphere and thalamus with minimal zone of hemorrhage, in the right pons showed on SWI images (Fig. 6). In the postoperative course, the patient was sedated for three days after which we weaned him off the respirator, on day 5 he was extubated. Of note is that he had a pseudoaneurysm (PSAN) of the right communal femoral artery which was treated with compression. On day 10 the patient was transferred back to the regional hospital with a recommendation of clopidogrel 75 mg/d and other indicated and supportive therapy. On follow-up, the patient was discharged home after 10 more days with dysarthria, mild di hemiparesis, and ataxia, his mRS score was 2.

DISCUSSION

Stroke, especially ischemic stroke represents an epidemic of the contemporary world population

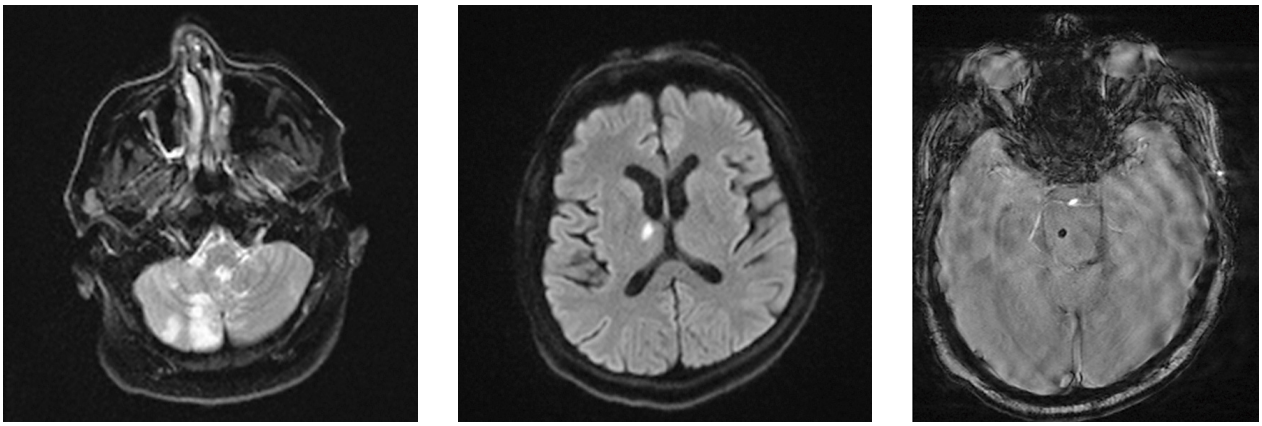

Fig. 6. *Control MRI showed acute ischemia of the left and right cerebellar hemisphere and thalamus with minimal zone of hemorrhage, in the right pons showed on SWI images.*

with a high rate of mortality and disability (18). Therefore, the goal of AIS treatment is aimed at achieving early reperfusion in order to prevent and reduce these consequences.

Thrombolytic therapy with r-tPA for AIS is well established AIS treatment for almost three decades such as mechanical thrombectomy (MT) in the last 10 years (1, 19).

Current guidelines for thrombolytic treatment of AIS pointed to a history of the previous stroke within 3 months as a contraindication to re-thrombolytic treatment, which has not been changed since the beginning of the use of r-tPA for AIS treatment (7,8,20). These recommendations are based on an assumed increased risk of sICH due to neurotoxicity, BBB disruption, dysfunction of the vascular basal lamina associated with re-administration of r-tPA in ERAIS, especially in the area of the former infarct which is presumed that is not yet recovered, as well as potentially higher risk of severe immune reactions (2-5,21,22). However, the results of a series of studies have shown that sICH occurs very rarely in the area of previous ischemic infarction. In addition, the pharmacokinetic properties of r-tPA exclude the possibility of a negative cumulative effect of readministration in ERAIS (2,4,5,17).

The risk of early AIS recurrence within 3 months is about 14.5%-18.3% according to data from the Oxfordshire Community Stroke Project (OCSP) (23,24). ERAIS is thought to be associated with higher mortality and poorer outcome which is strictly related to current guidelines for thrombolytic treatment and excludes a large number of patients who suffered an ERAIS for repeated intravenous thrombolysis (RIVT), regardless of the needs or possibility for MT, which also has an early risk of reocclusion (> 2%) with the need to repeat MT (25).

In assessing the risk and potential efficacy of RIVT, studies emphasized the importance of the residual neurological deficits, severity of the new ERAIS, and the findings of multimodal neuroimaging (15-17,26-28).

Recent clinical trials and recommendations for ERAIS treatment considered that mechanical thrombectomy is superior to systemic thrombolysis alone in patients with large vessel occlusion (LVO) (19, 20, 28-30).

But in situations when the primary stroke center is far away from the comprehensive stroke centre (CSC), it is necessary to repeat neuroimaging and seek telemedicine consultation with the designated „stroke team“ to assess the potential need to reapply thrombolysis before transport to CSC for possible MT (19,29). We demonstrated the efficacy of RIVT, in combination with the “the drip-and-ship” model for mechanical thrombectomy in addition to telemedicine consultation in our patient, in whom the RAIS was due to early reocclusion of the same artery from the dissected right vertebral artery, despite the best medical treatment (30-32). Our case with successful re-reperfusion therapy and good functional outcome as well as the results of previous studies support effective reperfusion treatment (repeated IVT and repeated MT) in patients with ERAIS, including prior multimodal neuroimaging modalities and a CSC “stroke team” telemedicine consultation for effective assessment and selection of patients. We also consider that depending on adequate assessment for RIVT, taking into account the previous neurological deficit and the severity of ERAIS estimated by NIHSS, there may be a greater pool of patients who can still benefit from RIVT treatment (17).

These results of the effectiveness of RIVT in ERAIS require an answer to the question posed by Wu in

his article, after revising the relevant publications "Is it time to reconsider the inclusion criteria and exclusion criteria of intravenous thrombolysis?" (26). In accordance with our clinical experience, we also believe that the current guidelines on contraindications for RIVT in ERAIS should be modified and changed, incorporating advanced multimodal neuroimaging techniques for safe and effective rethrombolytic treatment in selected patients. Additional research and larger studies should be directed to the revision of exclusion and inclusion criteria and recommendations for the repeated IVT in ERAIS.

CONCLUSION

Our case report suggests that repeated IV thrombolysis, followed by repeated mechanical thrombectomy may be safe and efficacious in patients with early recurrent ischemic stroke, including prior adequate multimodal neuroimaging techniques and CSC "stroke team" telemedicine consultation. We believe that consideration should be given to amending the guidelines for the use of IVT in the early recurrence of ischemic stroke in selected patients.

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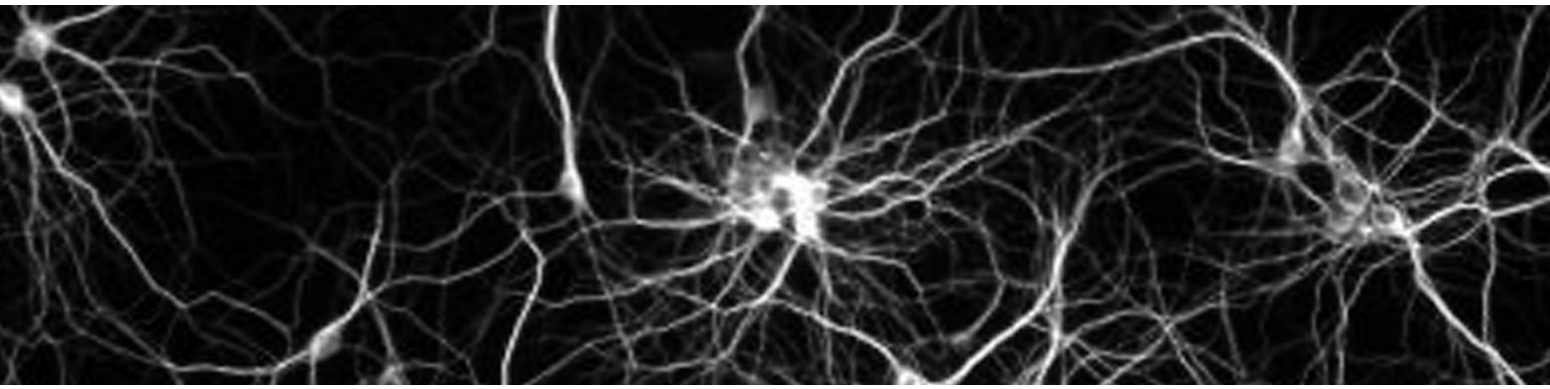

Tuberous sclerosis complex and epilepsy

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ABSTRACT - Tuberous sclerosis complex (TSC) is a multi-system neurocutaneous genetic condition with autosomal dominant inheritance caused by deletion, rearrangement, and inactivating mutation of tumor suppressor genes TSC1 or TSC2. This mutation causes the overactivation of the mammalian target of rapamycin (mTOR) signal pathway, responsible for cellular proliferation and inhibition of cellular apoptosis. Inactivation of one of the TSC genes results in hyperactivity of the mTOR pathway and the development of benign tumors or hamartomas in multiple organ systems, including skin, brain, eyes, heart, and kidneys. Clinical manifestations of TSC are protean in terms of severity and the range of tissues it can involve. Diagnosis is based on independent clinical and genetic criteria. Epilepsy is one of the main clinical manifestations and a significant cause of morbidity and mortality in TSC. Epileptic seizures occur in 70%-90% of patients with TSC and most frequently lead to the diagnosis of the condition. Epileptic seizures usually start within the first three years of life, typically as infantile spasms and focal seizures. However, all types of epileptic seizures can occur in TSC, and two-thirds of the cases develop into refractory epilepsy. Each symptom in TSC demands evaluation and management within the relevant clinical context as a consequence of the multi-system involvement. Treatment of TSC is symptomatic, although mTOR inhibitors have been groundbreaking due to their ability to target the molecular defect in the disorder.

Keywords: epilepsy, mTOR inhibitors, tuberous sclerosis complex

TUBEROUS SCLEROSIS COMPLEX AND EPILEPSY

Tuberous sclerosis complex (TSC) is a multi-system neurocutaneous genetic condition with autosomal dominant inheritance, characterized by hamartomas that affect multiple organs, including skin, central nervous system, heart, lungs, and kid-

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ney. It is also known as *epiloia* or Pringle-Bourneville phacomatosis. It was initially described in the 19th century by Virchow and von Recklinghausen, who identified hamartomas in the brain and heart during the necropsy of patients with seizures and mental retardation (1).

TSC affects approximately 1 in 6.000 to 10.000 individuals, although the variable penetrance and subtle presentation of the disease mean that the incidence may actually be higher (2). Central nervous system involvement is almost always present and represents a significant cause of morbidity and mortality for individuals afflicted with the TSC resulting in three characteristic brain malformations or lesions: cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs). The presence of cortical tubers, a subtype of focal cortical dysplasia, within the cerebral cortex and/or subcortical white matter is a hallmark histopathological characteristic of TSC in the brain (3). Focal cortical dysplasia comprises a spectrum of focal developmental malformations characterized by disruption of normal cytoarchitecture of the cerebral cortex. They are highly associated with medically intractable epilepsy. Approximately 80%-85% of TSC patients have at least one seizure in their lifetime, and nearly all patients develop epilepsy (1,4). In TSC are also presented developmental delay and neurobehavioral or neuropsychiatric disorders (e.g., autism spectrum disorder [ASD], hyperactivity, and anxiety) (1,3).

ETIOPATHOGENESIS

TSC occurs due to the deletion, rearrangement, and inactivating mutation of tumor suppressor genes TSC1 or TSC2, which produce abnormal proteins hamartin and tuberin, codified in the loci 9p34 and 16p13, respectively. The role of these genes consists of the regulation of cellular growth through the phosphatidylinositol 3-kinase signal pathway, inhibiting the mammalian target of rapamycin (mTOR). The complex hamartin/tuberin is an important inhibitor of tumor growth. These proteins suppress the activity of the mTOR pathway, responsible for cellular proliferation and inhibition of cellular apoptosis. Inactivation of one of the TSC genes results in hyperactivation of the mTOR pathway and the development of benign tumors or hamartomas in multiple organ systems, including skin, brain, eyes, heart, and kidneys. The brain is often the most severely affected organ (1,3). The neurological features of TSC reflect structural brain abnormalities. Histopathological examination of TSC brain specimens reveals cortical tubers, subependymal nodules, and SEGAs. Cortical tubers are focal developmental malformations of the cerebral cortex exhibiting loss of normal hexalaminar structure. They contain several abnormal structure elements including dysmorphic neurons (DNs), excessive numbers of astrocytes, and giant cells (GCs). Radiological studies demonstrated the presence of tubers in utero by 20 weeks gestation, suggesting that tubers form during embryonic cortical development. In contrast, subependymal nodules are benign proliferative lesions protruding from ventricular surface into the ventricular lumen and are believed to be asymptomatic. Subependymal nodules may undergo transformation into SEGAs, which are found in 10% of patients, and may lead to progressive hydrocephalus and death (5).

CLINICAL MANIFESTATION

Clinical manifestations of TSC can occur at any age, thereby making the diagnosis difficult. There is no typical disease presentation and the clinical presentation usually differs between pediatric and adult patients. Furthermore, variable penetrance of the genetic mutation causes a range of disease severity from very mild to severe, and in affected individuals, the condition can go undetected for years because many of the clinical manifestations of TSC lack specificity (6).

TSC is characterized by the multi-focal occurrence of benign tumors (hamartomas) and focal dysplastic lesions (hamartias) in various organs. In the vast majority of organs, these morphological lesions, especially tumors, are the sole cause of functional problems, such as dysmorphism, rupture, and pressure on the surrounding normal tissue. Despite the potential of TSC to involve any organ system in the body, some organs are more affected than others. Cutaneous manifestations represent the most common findings observed in TSC patients. They are detected in all ages and affect more than 90% of TSC patients (1). Hypomelanotic macules, shagreen patch, and/or facial angiofibromas are often the first clinical symptoms that prompt medical evaluation in childhood (3). TSC patients can also present with fibrous plaques in the forehead (20%) and ungual or gingival fibromas (20%) (1,6,7).

The characteristic TSC kidney lesion is the angiomyolipoma, a benign tumor composed of abnormal vasculature and immature smooth-muscle and

fat cells that affects 55%-75% of patients. Although these tumors are typically asymptomatic, they can result in life-threatening emergencies due to bleeding from spontaneous rupture of aneurysms when angiomyolipoma exceeds 3 cm in diameter (3,6).

Cardiac rhabdomyoma is one of the earliest manifestation of TSC, developing typically around weeks 22 to 28 of gestation. This tumor occurs in up to approximately 50%-70% of patients with TSC, primarily during the fetal and neonatal periods. These lesions are usually asymptomatic and tend to regress spontaneously with increasing age, however, in a small percentage of patients, they cause symptoms such as outflow obstruction, valvular dysfunction, or arrhythmia (6).

Many patients with TSC have brain dysfunction without an apparent causal relationship with anatomical lesions (8).

Abnormalities of the central nervous system associated with TSC typically manifest in childhood and can lead to problematic neurological and psychological issues, including epilepsy, cognitive deficits, and autism spectrum disorders (1,6). The main neurological manifestation of TSC is epilepsy, which occurs in 70%-90% of patients with TSC and most frequently leads to the diagnosis of the condition. Epileptic seizures usually start within the first three years of life, typically as infantile spasms and focal seizures. However, all types of epileptic seizures can occur in TSC and two-thirds of the cases develop into refractory epilepsy (1). Approximately 50% of children with TSC develop infantile spasms, a rapid-onset early childhood epilepsy syndrome that typically occurs in the first year of life as clusters of generalized flexor or extensor spasms, and can occur with numerous structural, metabolic, and genetic etiologies (9). A history of infantile spasms, seizure onset at a younger age, and refractory epilepsy have previously been shown to be associated with poor cognitive outcomes (10,11). Epilepsy is often resistant to antiepileptic drugs and in many cases can require neurosurgical treatment. The level of intelligence is variable among patients, ranging from normal to profound intelligence disorder present in more than half of patients and autism spectrum disorder in about half. Even patients with normal intelligence have a variety of behavioral, cognitive, and psychosocial problems, which are collectively called TSC-associated neuropsychiatric disorders. Approximately 10% of patients have SEGA, a benign tumor on the wall of the lateral ventricle. A large SEGA may cause hydrocephalus and clinical signs of increased intracranial pressure (6,8).

DIAGNOSIS

The International TSC Clinical Consensus Group reaffirms the importance of independent genetic diagnostic criteria and clinical diagnostic criteria. Identification of a pathogenic variant in TSC1 or TSC2 is sufficient for the diagnosis or prediction of TSC despite clinical findings. Genetic diagnosis of TSC prior to an individual meeting clinical criteria for TSC is beneficial to ensure that individuals undergo surveillance to identify manifestations of TSC as early as possible to achieve optimal clinical outcomes. Between 10%-15% of patients with TSC meeting clinical diagnostic criteria have no mutation identified by conventional genetic testing. Therefore, failure to identify a pathogenic variant in TSC1 or TSC2 does not exclude a diagnosis of TSC (2). The clinical and genetics diagnostic criteria are summarized in table 1.

Table 1. *Diagnostic criteria*

Major Criteria	Minor Criteria
Hypomelanotic macules (≥3; at least 5 mm diameter)	"Confetti" skin lesions
Angiofibroma (≥3) or fibrous cephalic plaque	Dental enamel pits (≥3)
Ungual fibromas (≥2)	Intraoral pits (≥2)
Shagreen patch	Retinal achromic patch
Multiple renal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangiomyomatosis*	
Angiomyolipomas (≥2)*	

Definite TSC: 2 major features or 1 major feature with 2 minor features

Possible TSC: either 1 major feature or ≥2 minor features

Genetic diagnosis: A pathogenic variant in TSC1 or TSC2 is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production)

*A combination of the 2 major clinical features LAM and angiomyolipoma without other features does not meet criteria for a definite diagnosis.

With the approval of the authors: Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, *et al.* Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021

TREATMENT AND MANAGEMENT

TSC treatment consists, above all, of the management of the symptoms caused by hamartomas and prophylactic measures to avoid loss of function of the affected organ (1,6). As a consequence of the multi-system involvement in TSC, each symptom demands evaluation and management within the relevant clinical context. mTOR inhibitors have been groundbreaking in the TSC world due to their ability to target the molecular defect in the disorder. Rapamycin mTOR inhibitors and their derivative everolimus have been studied in TSC patients since 2006 and are promising for the treatment of multiple tumors including renal angiomyolipomas, giant cell subependymal astrocytomas, and lymphangioleiomyomatosis, with secondary benefit on the cutaneous manifestations (1,11). However, animal models and clinical studies have shown that not all TSC-related symptoms benefit from mTOR inhibitors to the same extent. Neurological manifestations should be managed from birth to adulthood. Prevention of early-onset seizures, if possible, may improve patient's quality of life over the long term by reducing the morbidity often associated with epilepsy. Most used antiseizure medications for epilepsy in TSC are valproate, vigabatrin, levetiracetam, carbamazepine, lamotrigine, topiramate, oxcarbazepine, lacosamide, and clobazam (12). Vigabatrin is the first line of treatment for infantile spasms. Steroids and classic antiepileptic drugs (AEDs) are suitable for second line of treatment. Reading through the literature, retrospective studies showed that vigabatrin should be considered for other indications, for example in infants with focal seizures but also in children and adults with epileptic spasms and tonic seizures. Treatment based on the type of epileptic seizures is similar to that for patients without TSC, including the use of novel AEDs. Other options for poorly controlled or refractory epilepsy include consumption of a ketogenic diet, surgical excision of tubers, vagus nerve stimulation (VNS), and corpus callosotomy (3,6,7,11,13). Cannabidiol (CBD) is a non-psychoactive drug extracted from the cannabis plant. Several large, multicenter, double-blinded, placebo-controlled trials showed efficiency of CBD oil in Lennox-Gastaut syndrome and Dravet syndrome. A specific formulation of CBD has been evaluated in randomized controlled clinical trials to treat seizures in TSC and found to be effective and well-tolerated (2). So far, clinical studies showed that in patients with TSC and with a high baseline burden of treatment-resistant, primarily focal seizures, add-on CBD significantly reduced seizure frequency compared with placebo and the future role of CBD should still be more investigated. CBD is approved in the USA for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or TSC in patients who are aged one year and older, and in the European Union (13,14). Additionally, there is evidence to suggest that mTOR inhibitors may ameliorate or prevent seizures in TSC (3,6,11). After the discovery of the regulation of the mTOR pathway in the development of TSC tumors and with the advent of the target therapy using mTOR inhibitors, some promising studies have been highlighted, favoring the possibility of treating TSC patients according to the physiopathogenesis of the condition. Rapamycin is a natural macrolide isolated from *Streptomyces hygroscopius* in 1965, that binds specifically to mTOR, resulting in the inhibition of mTOR activity and finally promoting the inhibition of cellular growth. Monitoring for the development or progression of potentially life-treating condition in the central nervous system such as SEGA is also warranted. Patients should undergo regular brain imaging. Symptomatic or enlarging SEGAs should be surgically excised when possible. Everolimus therapy can be considered to reduce SEGA volume, especially for growing but asymptomatic SEGA, or for SEGA requiring intervention but are inoperable (6,11). Patients treated with everolimus for SEGAs had a clinically relevant reduction of their seizure frequency and improved quality of life (11).

Renal angiomyolipoma requires close monitoring and careful management in both childhood and adult life. Although it is often asymptomatic, the nature of angiomyolipoma with fragile aneurysmal blood vessels surrounded by soft adipose tissue can lead to spontaneous and severe renal hemorrhage (1,6). Sirolimus (rapamycin) and everolimus (a rapamycin analogue) have successfully been used to treat renal angiomyolipomas and SEGAs in studies in TSC patients. Everolimus recently received Food and Drug Administration (FDA) approval for treatment of SEGAs at any age, and for renal angiomyolipomas over the age of 18. Sirolimus also reduced lymphangioleiomyomatosis (LAM) growth in some, but not all patients (11).

From the dermatological point of view, multiple descriptive or surgical treatments were developed to decrease the development and remove facial angiofibromas such as dermaabrasion, surgical excision, electrocautery, and laser. These procedures tend to be uncomfortable for patient, need to be repeated periodically to avoid recurrence of the lesions and many times need to be associated with

other therapeutic methods in an attempt to optimize results (1,3). The timing of treatment is crucial for all involved organs' symptoms, and treatment during early critical windows has been necessary (7).

CONCLUSION

TSC is a multi-system disease in which epilepsy occurs in of 70%-90% cases. Furthermore, a third of patients with TSC develop refractory epilepsy. Although TSC is rare, it is one of the most common causes of genetic epilepsy in the pediatric population. The importance of early diagnosis, based on genetic testing and clinical manifestations, and treatment has significantly improved the clinical outcomes of the disease. Numerous clinical studies have confirmed that adequate pharmacological therapy, surveillance, and management of patients with TSC immediately after the disease is confirmed, significantly reduces the risk of epileptic seizures and the development of intellectual disability. Special emphasis was placed on researching the neurological manifestations of TSC, given that they, together with renal manifestations, were leading cause of morbidity and mortality in patients. Mammalian target of rapamycin inhibitors which act on the cause of the disease on the molecular level have gained advantage over conventional symptomatic treatment of symptoms.

Modern diagnostics, adequate monitoring, and use of mTOR inhibitor have significantly improved the quality of life, as well as the understanding of the role of the mTOR signaling pathway in epileptogenesis. However, TSC is still the subject of many ongoing scientific research and clinical studies.

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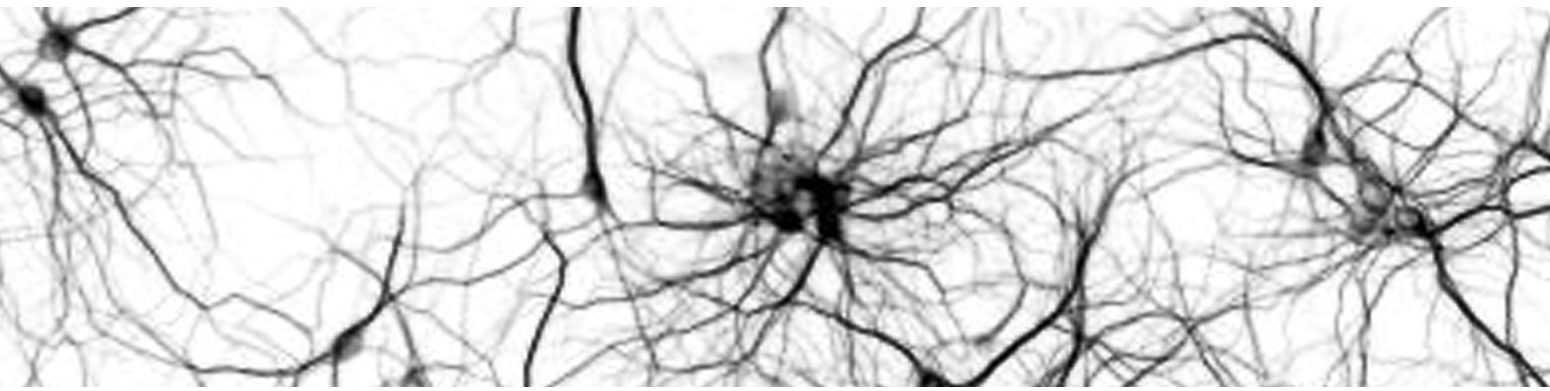

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