UDK 616.8

ISSN 2939-3027

Neurologia Croatica

SINCE 1953

NEUROL. CROAT. 2023 68 (2): 61-108

UDK 616.8

ISSN 2939-3027

Neurologia Croatica

SINCE 1953

OFFICIAL JOURNAL OF

Croatian Neurological Society
Croatian Neurosurgical Society

NEUROL. CROAT. 2023 68 (2): 61-108

NEUROLOGIA CROATICA (Vol. 1-24 "Neuropsihijatrija", Vol. 25-39 "Neurologija") Journal of Clinical Neuroscience published by University Department of Neurology, Zagreb University Hospital Center, School of Medicine, University of Zagreb, Zagreb, Republic of Croatia

Publisher: University of Zagreb, School of Medicine
University Hospital Center Zagreb, Department of Neurology
Kišpatićeva 12
HR-10000 Zagreb, Croatia
Phone: + 385 1 2388 310
Fax: + 385 1 2376 021
E-mail: neurologiacroatica@kbc-zagreb.hr
Web address: neurologiacroatica.hr

ISSN: 2939-3027

Journal comes out: Semi-annual

Journal is funded by: Hrvatski liječnički zbor - Hrvatsko neurološko društvo
Croatian Medical Association – Croatian Neurological Association

Proofreading: Ana Topolovac, mag. polit.

Typesetting by: DENONA d.o.o., Getaldićeva 1, Zagreb

Programming and Administration: BelSoft d.o.o.
Šulekova 2
10 000 Zagreb
Antun Baković, antun@belsoft.hr

Personal Data Protection Officer: BelSoft d.o.o.
Šulekova 2
10 000 Zagreb - CROATIA

For the Personal Data Protection Officer Antun Baković, antun@belsoft.hr
+385 98 448255

Review process The editorial process begins by accepting the paper, electronically, into the journal's editorial office. The editors confirm the author's receipt of the paper. After receiving the paper, a review process follows to decide whether the received paper will be published in a journal. The paper is first reviewed by one of the members of the editorial board, and if the first round of review passes, one or more independent reviewers are given the review. If a positive opinion is obtained, the paper can be published. If the reviewers (both or only one) do not give a positive opinion, the paper is returned to the author to be revised in accordance with the reviewers' recommendations. The editor-in-chief of the journal may accept the paper for publication regardless of the reviewer's recommendation.

Contents

67 | **Editorial**
Mario Habek

NEUROLOGICAL REVIEWS

69 | **Spinal muscular atrophy associated with progressive myoclonic epilepsy – clinical, genetic, and biochemical variability: selected literature review**
Marin Begović, Željka Petelin Gadže, Ervina Bilić

77 | **Definition and historical overview of posterior reversible encephalopathy syndrome**
Kim Bogdan Veljković, Iva Benić, Zdravka Poljaković-Skurić

CASE REPORTS

87 | **Bilateral facial palsy and left abducens palsy in a patient with neuroborreliosis**
Paula Božić, Romana Perković, Nataša Klepac, Fran Borovečki

91 | **Combined surgical and Gamma Knife treatment of extremely rare hypopharyngeal squamous cell carcinoma brain metastasis in the eloquent region**
Manuela Frančić, Niko Njirić, Biljana Đapić Ivančić, Antonija Jakovčević, Vesna Bišof, Romana Perković, Jakob Nemir

95 | **Anesthesiological approach to intrathecal baclofen overdose**
Monika Kocman Panić, Jadranka Premužić, Ivan Koprek, Nenad Kudelić, Renata Krobot, Anita Lukić, Slobodan Mihaljević

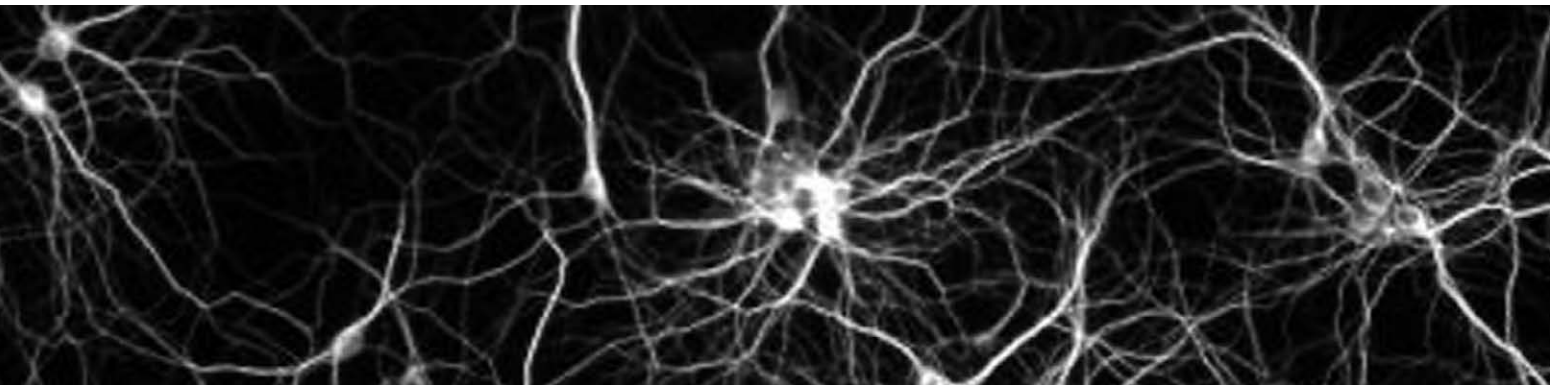
98 | **Marchiafava–Bignami disease: a rare but not forgotten complication of chronic alcoholism**
Žana Kralj, Josipa Fiamengo, Gordana Glavina, Krešimir Dolić, Gordan Džamonja

IMAGES IN NEUROLOGY

102 | **CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids**
Denis Čerimagić, Ervina Bilić

105 | **Authors index for volume 68/2023**

107 | **Instructions to authors**



Editorial

Dear Readers and Colleagues,

Welcome to the second issue of Neurologia Croatica in 2023.

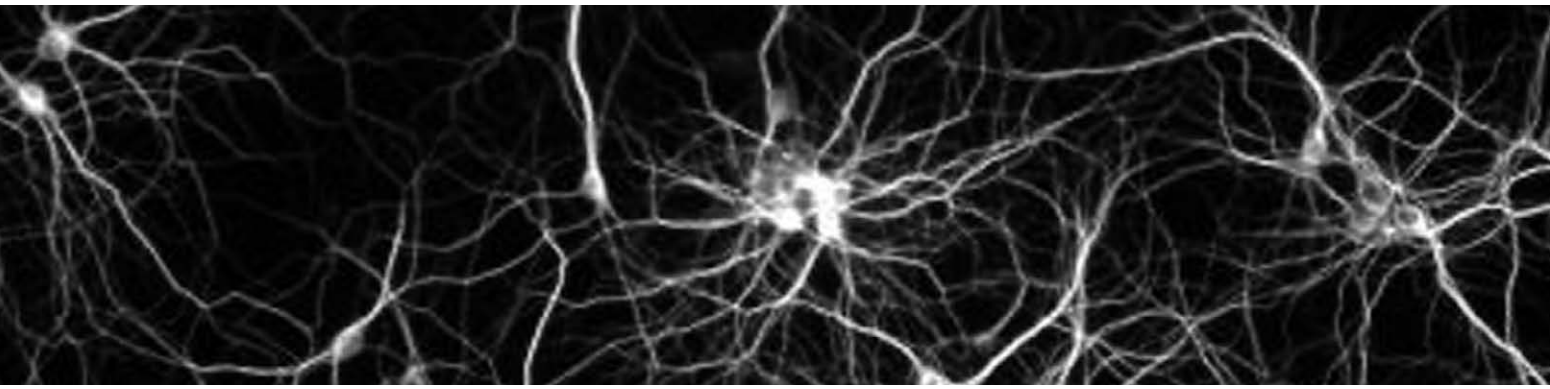
We have finished the first successful year under the new editorial board of Neurologia Croatica.

In this issue of the journal, we bring you two neurological reviews on rare neurological diseases: posterior reversible encephalopathy syndrome and spinal muscular atrophy associated with progressive myoclonic epilepsy. Furthermore, several interesting case reports indicate difficulties in the diagnosis and treatment of people with neurological diseases in everyday clinical practice are presented. A very educational case by Prof. Džamonja from University Hospital Center Split describes Marchiafava–Bignami disease which is a rare but not forgotten complication of chronic alcoholism. In that regard, we invite young neurologists in training to submit preliminary results of their research and interesting case reports to our journal.

We are grateful to all reviewers who completed their reviews in 2023: Ervina Bilić, Svetlana Tomić, Jadranka Sekelj Fureš, Hrvoje Bilić, Marina Boban, Gordan Grahovac, Ivica Bilić, Fadi Almahariq, Mihael Mišir, Tereza Gabelić, and Gregor Brecl Jakob. The quality of the journal's review process is extremely important to the success of Neurologia Croatica and so the contributions of scientific expertise of our reviewers to this process are most appreciated.

In the end, I hope you will enjoy reading this issue and invite you to submit your next article to Neurologia Croatica.

Mario Habek
Editor-in-chief



Spinal muscular atrophy associated with progressive myoclonic epilepsy – clinical, genetic, and biochemical variability: selected literature review

Marin Begović[1], Željka Petelin Gadže[2], Ervina Bilić[3]

ABSTRACT – Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is a rare inherited autosomal recessive disease related to mutations of the ASAH1 gene, serving as an allelic disorder to Farber disease (FD). Main characteristics of a substantial proportion of patients suffering from SMA-PME are the onset of predominantly proximal muscular weakness, later appearance of a generalized epilepsy with absences and myoclonic seizures, cognitive impairment of variable degree, and a progressive course of the disease with death occurring mostly in late adolescence. The ASAH1 gene encodes the acid ceramidase, an enzyme involved in the transformation of ceramide into sphingosine and a free fatty acid in the lysosomes. Ceramides affect antiproliferative processes such as growth inhibition, apoptosis, differentiation, and senescence. Ceramides are the precursors to complex sphingolipids, which are crucial for normal functioning of the brain in development as well as the mature brain. The nervous system is greatly impacted by acid ceramidase deficiency, with both the central and/or peripheral nervous systems being affected. Successful measurement of the C26-ceramide and its isomers in a stable and easily accessible sample type, such as dried blood spots, may allow this measurement to attain widespread use for the screening of ASAH1-related disorders. Discovery of the genetic cause responsible for the onset of the disease has set the foundation for the

[1] University of Zagreb School of Medicine, Zagreb, Croatia

[2] Department of Neurology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Affiliated to ERN EpiCARE

[3] Department of Neurology, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Referral Center of the Ministry of Health of the Republic of Croatia for Neuromuscular diseases, and Clinical Electromyoneurography

development of novel therapeutic strategies, including enzyme replacement therapy, pharmacological chaperone therapy, and gene therapy each with its own benefits and limitations.

Keywords: ASAH1, ceramide, progressive myoclonic epilepsy, sphingosine, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA) is a group of genetically and clinically heterogenous syndromes inherited by different forms of inheritance pathways, including autosomal dominant, autosomal recessive, and X-linked (1). The most frequent form is inherited as an autosomal-recessive trait resulting from changes in survival of motor neuron 1 (SMN1) located in the anterior horns of the spinal cord and brainstem (2). On a global level, SMA is the leading cause of death due to a genetic disorder and, after cystic fibrosis, the second most common autosomal recessive disorder (3). SMA is primarily caused by homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. Consequently, the disease was called 5q-SMA (4). The clinical picture is mainly dominated by diffuse muscular atrophy, although some patients can also show atypical clinical features including oculomotor palsy, epilepsy, olivopontocerebellar atrophy, and multiple arthrogryposis (5). Rare causes of SMA, which approximate for around 4% of all cases, are called non-5q-SMA (4). Of several different genes, which have been found to be associated with non-5qSMA, N-Acylsphingosine Amidohydrolase 1 (ASAH1) gene is presumed to be the leading cause of SMA associated with the clinical picture of progressive myoclonic epilepsy (PME) (6).

PME is a diverse group of epilepsies marked by myoclonic and generalized seizures associated with progressive neurological deterioration. PME can affect individuals of any age group, but it usually starts in late childhood or adolescence (7). PME is thought to be responsible for up to 1% of epileptic syndromes in children and adolescents worldwide. PME is characterized by a mix of positive and negative myoclonus. PME can occur in the pure form such as Lafora disease or in combination with other clinical pictures as in Unverricht-Lundborg type disease (ULD), myoclonic epilepsy with ragged red fibers (MERRF), sialidosis, lysosomal storage disorders such as neuronal ceroid lipofuscinoses (NCLs), neuroserpinosis, myoclonic epilepsy, and ataxia due to potassium (K+) channel mutation (MEAK), action myoclonus renal-failure syndrome (AMRF), and spinal muscular atrophy associated with progressive myoclonus epilepsy (8).

Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is a rare inherited autosomal recessive disease related to mutations of the ASAH1 gene, serving as an allelic disorder to Farber disease (FD) (9). Although FD and SMA-PME are generally considered two phenotypically distinct diseases, there have been multiple described cases of patients who presented with phenotypic features of both FD and SMA-PME. Authors of those cases demonstrated that FD and SMA-PME are not always distinct diseases, but rather part of an evolving phenotypic spectrum (10-12).

SMA-PME was first clinically reported by Jankovic and Rivera in 1979. who described three subjects showing slight mental retardation and adult-onset myoclonic epilepsy combined with predominantly distal signs of SMA (13). Zhou *et al.* determined a homozygous missense mutation in exon2 of the ASAH1 gene (c.125C > T [p.Thr42Met]) as the likely cause of SMA-PME in 2012. (6). Discovery of the genetic cause responsible for the onset of the disease has set the foundation for the development of both gene and enzymatic replacement therapies.

CLINICAL PRESENTATION OF SMA-PME PATIENTS

An overview of all patients reported in the literature, including those described before the discovery of the genetic cause, identified the main characteristics of a substantial proportion of patients suffering from SMA-PME. Those characteristics are the onset of predominantly proximal muscular weakness, later appearance of generalized epilepsy with absences and myoclonic seizures, cognitive impairment of variable degree, and a progressive course of the disease with death occurring mostly in late adolescence (6,11-24). Progressive myoclonic seizures, which occur mostly in late childhood and are a hallmark of the disease, are characterized by jerking of the upper limbs, myoclonic status, action myoclonus, and eyelid myoclonus (24).

In some cases, epilepsy presents itself as the first symptom, mostly associated with drug refractoriness and the onset of severe incapacity, followed

some years later by subtle muscular deterioration (19, 23). Certain cases present with myoclonic epilepsy as the first symptom and have a proven ASAH1 mutation discovered on genetic testing but without findings of muscle atrophy (22).

The age of onset of symptoms can range from childhood, beginning at the age of two up to late adolescence. Childhood onset is frequently marked by severe muscle wasting, uncontrolled epileptic seizures, and a dismal evolution, with death occurring at a young age, often due to respiratory complications (16). In certain cases, where symptoms occur at a very young age, there is a more complex clinical picture including abnormal eye movements, pronounced cognitive impairment, and recurrent lung infections (16,20). It has been presumed that individuals who present with symptoms at the older age often show a slower and benign evolution, without cognitive impairment, and with epilepsy and myoclonus which better responds to antiepileptic drugs (20).

Generalized tremor, cognitive decline, and sensorineural hearing loss are also among the manifestations of SMA-PME (20). Patients sporadically present with cortical myoclonus which mimics tremor, and this may explain the description of associated tremor in several reported cases of the disease (23). In some cases, cognitive decline, presented as learning difficulties and speech decline, was the first symptom observed which provoked further investigation of the involved patient (23). Lee *et al.* presented a patient suffering from a specific mutation variant of the ASAH1 gene whose initial symptom was sensorineural hearing loss. Several additional patients with the same mutation variant had confirmed sensorineural hearing loss later in the diagnostic approach (23). Certain patients present with both SMA-PME and FD phenotypes resulting from ASAH1 mutation. Teoh *et al.* described a patient with both phenotypes who presented with polyarticular arthritis at 3 years of age followed by motor neuron disease without seizures (10). Lee *et al.* described a patient with both phenotypes who presented with gait difficulty, tremulousness, and leg pain at 3 years of age, for whom performed muscle biopsy showed marked recent denervation and chronic denervation pattern consistent with SMA. Described patient never had a clinical event concerning for seizures (11). Axente *et al.* described a patient with an overlapping phenotype of SMA-PME and FD who presented with global motor deficit, retractions of elbows and knees, and subcutaneous nodules at the interphalangeal level (12).

GENETIC CAUSE OF THE DISEASE

SMA-PME is inherited as an autosomal recessive trait. Genome-wide linkage analysis combined with exome sequencing revealed mutations in the ASAH1 gene, located on chromosome 8, which were responsible for the disease (6). Zhou *et al.* found the same missense mutation in exon 2 of ASAH1 (c.125C>T; p.Thr42Met) in all the affected individuals included in the study. The p.Thr42Met missense substitution was predicted to be damaging since it impacted an evolutionarily conserved amino acid among diverse species. To analyze the effect of ASAH1 loss-of-function *in vivo*, a morpholino antisense oligonucleotide of the ASAH1 ortholog was used to knock down ASAH1 in zebrafish embryos. Analysis of this model showed a marked abnormality in motor neuron axonal branching coupled with a considerable increase in apoptosis in the spinal cord (6).

PATHOGENESIS OF SMA-PME LINKED TO ASAH1 GENE MUTATIONS

The ASAH1 gene encodes the ASAH protein (N-acylsphingosine amidohydrolase 1, N-acylsphingosine deacylase, or acid ceramidase). Acid ceramidase is an enzyme involved in the transformation of ceramide into sphingosine and a free fatty acid (FFA) in the lysosomes, as well as the reverse process of ceramide synthesis from sphingosine and FFA under different pH conditions (19). It has recently been discovered that acid ceramidase interacts with fatty acid amide hydrolase and N-acylethanolamine-hydrolyzing acid amidase to degrade N-acylethanolamine (NAE) to ethanolamine and FFA at pH 4.5, with a possible preference for NAEs over ceramide, despite the fact that these molecules are present in much lower abundance in cells (25). Ceramide, ceramide-1-phosphate (C1P), sphingosine, sphingosine-1-phosphate (S1P), and NAEs are all bioactive lipids involved in cellular signaling, exhibiting a variety of biologic functions via different receptors (26). Ceramides are the precursors to complex sphingolipids, which are crucial for normal functioning of the brain in development as well as the mature brain. Ceramides affect antiproliferative processes such as growth inhibition, apoptosis, differentiation, and senescence (26,27). Ceramides have also been shown to be critical regulators of the cell cycle, regulating morphological transformations and checkpoints, binding to transcription factors, and altering mitotic spindle assembly (28).

Table 1. *Review of selected literature*

	Zhou *et al.*,2012	Rubboli *et al.*,2015	Lee B.H. *et al.*,2020	Axente M *et al.*,2021	Karimzadeh P *et al.*,2022	Lee M.M. *et al.*,2022
Number of cases described	6 (Family D=3, Family ITA=2, Family ITB=1)	3	1	1	5	6
SMA						
Ability to walk(m.)	14 (Family D) Normal (Families ITA and ITB)	Normal (Cases 1,3) 17 (Case 2)	17	24	Normal	Normal
Age of onset of weakness(y.)	5 to 6	2.4 to 6	3	1	1.5 to 7	2 to 15
Predominant muscle symptoms	Proximal weakness (Family D) Progressive muscle weakness (Families ITA and ITB)	Progressive muscle weakness (Cases 1,2) Mild proximal weakness (Case 3)	Progressive muscle weakness	Progressive muscle weakness	Proximal weakness	Progressive muscle weakness
EMG result	Chronic denervation process (Families D and ITB) Denervation-reinnervation process (Family ITB)	Chronic denervation process	Chronic denervation process	Chronic denervation process	Chronic denervation and neurogenic process	Chronic denervation process
PME						
Age of onset	7 (Family D) 12 (Family ITA) 10 (Family ITB)	8 (Case 1) 3 (Case 2) 12 (Case 3)	/	/	/ (Cases 1-3,5) 1st seizure 1-year-old and again at 7-year-old (Case 4)	9 (Case 1) 15 (Case 2) 6 (Case 3) 10 (Case 4) 3 (Case 5) 13 (Case 6)
Type of seizures	Myoclonic seizures (Family D) Generalized epileptic seizures with myoclonic jerks (Family ITA) Impairment of consciousness with myoclonic jerks (Family ITB)	Impairment of consciousness with myoclonic jerks (Case 1) Staring and myoclonic jerks (Case 2) Myoclonic seizures and absence seizures (Case 3)	/	/	/ (Cases 1-3,5) Myoclonic seizures (Case 4)	Generalized tonic-clonic seizures (Cases 1,2,4) Myoclonic seizures (Cases 1-6) Absence seizures (Cases 2,3)

Table 1. *Continued*

	Zhou *et al.*,2012	Rubboli *et al.*,2015	Lee B.H. *et al.*,2020	Axente M *et al.*,2021	Karimzadeh P *et al.*,2022	Lee M.M. *et al.*,2022
EEG	Subcortical myoclonic epileptiform abnormalities sensitive to hyperventilation (Family D) Diffuse bursts of sharp waves and poly-spike and wave complexes (Family ITB) Not reported (Family ITA)	Bursts of generalized spike- and polyspike and-wave complexes associated with either positive or negative myoclonic phenomena	Normal	Frequent generalized slow waves, rarely focalized, with the left side more affected than the right one	Normal (Cases 1-3,5) Bilateral Spike and wave discharges (Case 4)	Bursts of generalized spike-slow wave (Case 1) Generalized spike and polyspike -wave discharges (Cases 2-5) Multiple episodes of epileptic myoclonus (Case 6)
Brain MRI	Normal	Normal (Cases 1,3) Diffuse supratentorial and subtentorial cortical atrophy (Case 2)	Normal	Not reported	Normal	Not reported (Cases 1-4,6) Generalized cerebral atrophy (Case 5)
ASAH1 MUTATION						
Nucleotide	c.125C>T homozygous (Families D and ITA) ASAH1 deletion (Family ITB)	c.125C>T; homozygous (Case 1) c.223_224insC; c.125C>T (Case 2) c.177C>G; c.456A>C (Case 3)	c.966-2A>G c.1127C>T	c.458_459del; c.1226T>C); c.35G>C;	c.109C>A; homozygous (Cases 1,2) c.125C>T; homozygous (Cases 3-5)	C.124A>G; c.536C>T (Case 1) c.125+1G>A; c.456A>C (Case 2) c.125C>T; homozygous (Case 3) c.456A>C; c.918-2A>G (Case 4) c.109C>A; c.410_411del (Case 5) c.186G>A; c.456A>C (Case 6)
Protein	p.Thr42Met	p.Thr42Met (Case 1) p.Val75Alafs*25; p.Thr42Met (Case 2) p.Tyr59*; p.Lys152Asn (Case 3)	(splice variant) p.Thr376Ile	p.Tyr153*; p. Ile409Thr; p.Arg12Pro;	p.Pro37 Thr (Cases 1,2) p.Thr42Met (Cases 3-5)	p.Thr42Ala; p.Thr179Ile (Case 1) (splicing variants) (Case 2) p.Thr42Met (Case 3) (splicing variants) (Case 4) p.Pro37Thr; p.Tyr137* (Case 5) p.Trp62* (Case 6)
Acid ceramidase activity (% of NV)	32 %	Not reported	<1 %	Not reported	Not reported	4.1% to 13.1%

Y.: year; m.: month; NV: normal value

The nervous system is greatly impacted by acid ceramidase deficiency, with both the central and/or peripheral nervous systems being affected. In a case described by Levade *et al.,* post-mortem analysis of two sisters suffering from ASAH1 mutation and symptoms of central nervous system affection revealed that both sisters displayed neuronal loss, histiocytic infiltration, and vacuolization of neuronal cytoplasm (29). It has been considered that the hypotonia, atrophy, and muscle weakness found in many patient cases of ASAH1-related diseases are caused by the pathology in the anterior horn cells and peripheral neuropathy (30). Improved genotype-phenotype correlation understanding should result from a more thorough comprehension of acid ceramidase activity in the subcellular domain (31).

BIOMARKER C26-CERAMIDE

In a study designed by Mahmoud *et al.,* the novel biomarker C26-ceramide and its isomers were assayed in dried blood spots of seven children using liquid chromatography tandem mass spectrometry. Both the levels of the total C26-ceramide and the transC26-ceramide isomer showed 100% sensitivity for the detection of patients with ASAH1 variants. Authors further detected a positive correlation between the rate of disease progression in those seven patients and the levels of the total-C26-ceramide, however, the correlation did not reach statistical significance due to a limited number of patients (22).

The total and trans- isomer of C26-ceramide, which were extremely sensitive as biomarkers for the detection of ASAH1-related disorders for symptomatic patients in a study originated by Mahmoud *et al.*, may strengthen the set of resources for diagnosing ASAH1-related diseases. Successful measurement of the C26-ceramide and its isomers in a stable and easily accessible sample type, such as dried blood spots, may allow this measurement to attain widespread use for the screening of ASAH1- related disorders (22).

THERAPEUTIC APPROACH

There is currently no treatment for acid ceramidase deficiency. Symptom management is the primary emphasis of treatment methods. Treatment is usually individualized on a case-by-case basis. In addition to general palliative care, antiepileptic medications are typically administered to patients as their initial form of treatment (32). Physical therapy and psychotherapy are also incorporated into treatment plans (12). Many questions about the cause, diagnosis, and therapy of acid ceramidase deficiency still exist despite recent advancements. Research continues to describe novel, expansive roles demonstrated by acid ceramidase, further revealing its complexity. Comparing and contrasting current therapeutic potentials for acid ceramidase deficiency include enzyme replacement therapy, pharmacological chaperone therapy, and gene therapy, each with its own benefits and limitations. Further clinical research is needed to demonstrate the optimal therapeutic approach for patients suffering from SMA-PME (33).

CONCLUSION

Due to a wide range of clinical presentations and its rarity, acid ceramidase deficiency may often be misinterpreted as other, more well-known disorders which results in a difficult initiation of proper treatment strategy. The rapid progression of SMA-PME makes the correct initial diagnosis crucial for effective treatment and management. Further clinical research is needed to better understand the variable genotype-phenotype correlation of the disease and to find the optimal therapeutic approach for patients suffering from SMA-PME.

REFERENCES

1. Burr P, Reddivari AKR. Spinal Muscle Atrophy. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
2. Lefebvre S, Bürglen L, Frézal J, Munnich A, Melki J. The role of the SMN gene in proximal spinal muscular atrophy. Hum Mol Genet. 1998;7 (10):1531-1536. doi:10.1093/hmg/7.10.1531.
3. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015;33(4):831-846. doi:10.1016/j.ncl.2015.07.004
4. Verhaart IEC, Robertson A, Wilson IJ, *et al.* Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017;12(1):124. doi:10.1186/s13023-017-0671-8
5. Zerres K, Rudnik-Schöneborn S. 93rd ENMC international workshop: non-5q-spinal muscular atrophies (SMA) - clinical picture (6-8 April 2001, Naarden, The Netherlands). Neuromuscul Disord. 2003;13(2):179-183. doi:10.1016/s0960-8966(02)00211-0

6. Zhou J, Tawk M, Tiziano FD, *et al.* Spinal muscular atrophy associated with progressive myoclonic epilepsy is caused by mutations in ASAH1. Am J Hum Genet. 2012;91(1):5-14. doi:10.1016/j.ajhg.2012.05.001
7. Petelin Gadže Ž, Poljaković Z, Nanković S, Šulentić V. Epilepsija: dijagnostički i terapijski pristup. Zagreb: Medicinska naklada; 2019.
8. Orsini A, Valetto A, Bertini V, *et al.* The best evidence for progressive myoclonic epilepsy: A pathway to precision therapy. Seizure. 2019;71:247-257. doi:10.1016/j.seizure.2019.08.012
9. Yu FPS, Amintas S, Levade T, Medin JA. Acid ceramidase deficiency: Farber disease and SMA-PME. Orphanet J Rare Dis. 2018;13(1):121. doi:10.1186/s13023-018-0845-z
10. Teoh HL, Solyom A, Schuchman EH, *et al*. Polyarticular Arthritis and Spinal Muscular Atrophy in Acid Ceramidase Deficiency. Pediatrics. 2016;138(4):e20161068. doi:10.1542/peds.2016-1068
11. Lee BH, Mongiovi P, Levade T, Marston B, Mountain J, Ciafaloni E. Spinal muscular atrophy and Farber disease due to ASAH1 variants: A case report. Am J Med Genet A. 2020;182(10):2369-2371. doi:10.1002/ajmg.a.61764
12. Axente M, Shelby ES, Mirea A, *et al*. Clinical features and genetics in non-5q spinal muscular atrophy caused by acid ceramidase deficiency. J Med Life. 2021;14(3):424-428. doi:10.25122/jml-2021-0147
13. Jankovic J, Rivera VM. Hereditary myoclonus and progressive distal muscular atrophy. Ann Neurol. 1979;6(3):227-231. doi:10.1002/ana.410060309
14. Lance JW, Evans WA. Progressive myoclonic epilepsy, nerve deafness and spinal muscular atrophy. Clin Exp Neurol. 1984;20:141-151.
15. Marjanovic B, Todorovic S, Dozic S. Association of progressive myoclonic epilepsy and spinal muscular atrophy. Pediatr Neurol. 1993;9(2):147-150. doi:10.1016/0887-8994(93)90053-f
16. Haliloglu G, Chattopadhyay A, Skorodis L, *et al.* Spinal muscular atrophy with progressive myoclonic epilepsy: report of new cases and review of the literature. Neuropediatrics. 2002;33(6):314-319. doi:10.1055/s-2002-37087
17. Striano P, Boccella P, Sarappa C, Striano S. Spinal muscular atrophy and progressive myoclonic epilepsy: one case report and characteristics of the epileptic syndrome. Seizure. 2004;13(8):582-586. doi:10.1016/j.seizure.2004.01.008
18. Temucin CM, Buyukserbetci G, Ozdamar SE, Saygi S. A rare phenotype: progressive myoclonic epilepsy with lower motor neuron involvement. Epilepsia. 2008;49(10):1809-1812. doi:10.1111/j.1528-1167.2008.01651.x
19. Dyment DA, Sell E, Vanstone MR, *et al*. Evidence for clinical, genetic and biochemical variability in spinal muscular atrophy with progressive myoclonic epilepsy. Clin Genet. 2014;86(6):558-563. doi:10.1111/cge.12307
20. Rubboli G, Veggiotti P, Pini A, *et al*. Spinal muscular atrophy associated with progressive myoclonic epilepsy: A rare condition caused by mutations in ASAH1. Epilepsia. 2015;56(5):692-698. doi:10.1111/epi.12977
21. Filosto M, Aureli M, Castellotti B, *et al.* ASAH1 variant causing a mild SMA phenotype with no myoclonic epilepsy: a clinical, biochemical and molecular study. Eur J Hum Genet. 2016;24(11):1578-1583. doi:10.1038/ejhg.2016.28
22. Mahmoud IG, Elmonem MA, Zaki MS, *et al.* ASAH1-related disorders: Description of 15 novel pediatric patients and expansion of the clinical phenotype. Clin Genet. 2020;98(6):598-605. doi:10.1111/cge.13834
23. Lee MM, McDowell GSV, De Vivo DC, et al. The clinical spectrum of SMA-PME and in vitro normalization of its cellular ceramide profile. Ann Clin Transl Neurol. 2022;9(12):1941-1952. doi:10.1002/acn3.51687
24. Karimzadeh P, Najmabadi H, Lochmuller H, *et al.* Five patients with spinal muscular atrophy-progressive myoclonic epilepsy (SMA-PME): a novel pathogenic variant, treatment and review of the literature. Neuromuscul Disord. 2022;32(10):806-810. doi:10.1016/j.nmd.2022.08.002
25. Tsuboi K, Tai T, Yamashita R, *et al.* Involvement of acid ceramidase in the degradation of bioactive N-acylethanolamines. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866(9):158972. doi:10.1016/j.bbalip.2021.158972
26. Futerman AH, Hannun YA. The complex life of simple sphingolipids. EMBO Rep. 2004;5(8):777-782. doi:10.1038/sj.embor.7400208
27. Hannun YA, Obeid LM. Principles of bioactive lipid signalling: lessons from sphingolipids. Nat Rev Mol Cell Biol. 2008;9(2):139-150. doi:10.1038/nrm2329
28. Hawkins CC, Jones AB, Gordon ER, *et al.* Targeting Acid Ceramidase Inhibits Glioblastoma Cell Migration through Decreased AKT Signaling. Cells. 2022;11(12):1873. doi:10.3390/cells11121873

29. Levade T, Sandhoff K, Schulze H, Medin JA. Acid Ceramidase Deficiency: Farber Lipogranulomatosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019.

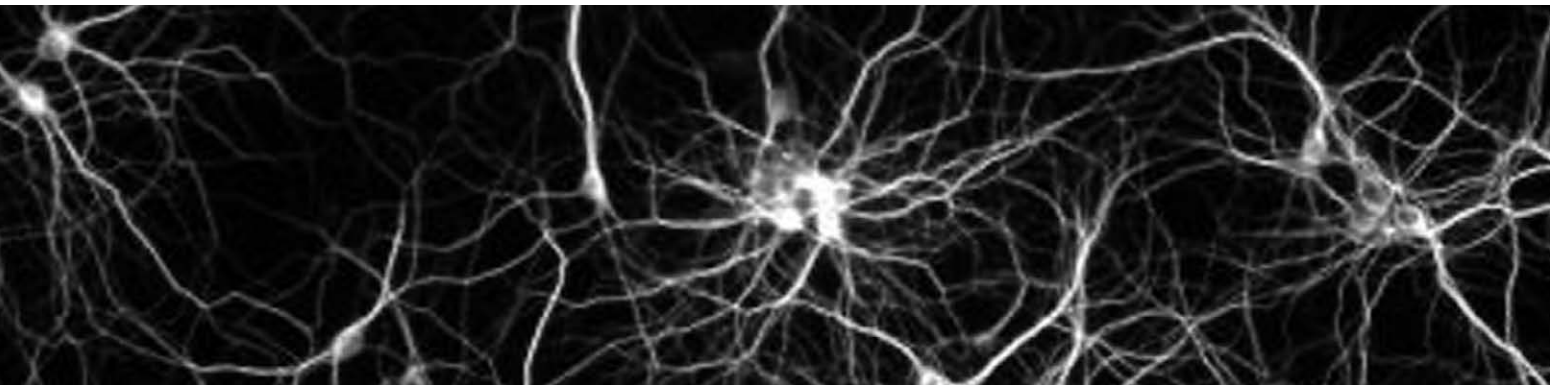
30. Sikora J, Dworski S, Jones EE, *et al.* Acid Ceramidase Deficiency in Mice Results in a Broad Range of Central Nervous System Abnormalities. Am J Pathol. 2017;187(4):864-883. doi:10.1016/j.ajpath.2016.12.005

31. Topaloglu H, Melki J. Spinal muscular atrophy associated with progressive myoclonus epilepsy. Epileptic Disord. 2016;18(S2):128-134. doi:10.1684/epd.2016.0858

32. Oguz Akarsu E, Tekturk P, Yapici Z, Tepgec F, Uyguner ZO, Baykan B. Eyelid myoclonic status epilepticus: A rare phenotype in spinal muscular atrophy with progressive myoclonic epilepsy associated with ASAH1 gene mutation. Seizure. 2016;42:49-51. doi:10.1016/j.seizure.2016.09.007

33. Kleynerman A, Rybova J, Faber ML, McKillop WM, Levade T, Medin JA. Acid Ceramidase Deficiency: Bridging Gaps between Clinical Presentation, Mouse Models, and Future Therapeutic Interventions. Biomolecules. 2023;13(2):274. doi:10.3390/biom13020274

Address for correspondence: Marin Begović; E-mail: marinbegovic13598@gmail.com



Definition and historical overview of posterior reversible encephalopathy syndrome

Kim Bogdan Veljković[1], Iva Benić[1], Zdravka Poljaković-Skurić[2]

ABSTRACT – Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiographic syndrome characterized by nonspecific neurological symptoms and characteristic imaging findings of symmetrical usually posterior-predominant cerebral white matter vasogenic oedema, although other regions of the brain may be affected in atypical forms of PRES. There are numerous causes of PRES. The most common conditions associated with it are moderate to severe hypertension, preeclampsia, and eclampsia, the use of immunosuppressant and cytotoxic drugs, autoimmune disorders, bone marrow, stem cell or solid organ transplantation, infection with sepsis and shock, and acute or chronic kidney disease. The precise pathophysiological mechanism behind PRES has yet to be fully clarified. The hypertensive and cerebral hyperperfusion theory proposes the loss of autoregulation in the posterior circulatory area of the cerebrovascular system due to large and sudden increases in blood pressure as the main cause. The endothelial dysfunction theory proposes endothelial injury caused by circulating toxins and the consequential increased permeability of the blood-brain barrier as the primary cause of the development of vasogenic oedema. Clinical presentation is nonspecific. The most common clinical presentation includes headache and impaired visual acuity, and in more severe cases visual loss, epileptic seizures, altered mental status, and altered levels of consciousness. T2-weighted/FLAIR sequences on magnetic resonance imaging (MRI) play a fundamental role in the diagnosis of PRES. The treatment is aimed at eliminating the cause if possible. PRES is usually reversible, and prognosis is good if the cause is recognized and removed.

Keywords: Posterior reversible encephalopathy syndrome, PRES, magnetic resonance imaging, vasogenic oedema, hypertension

[1] Community Health Center Zagreb – East, Zagreb, Croatia
[2] School of Medicine, University of Zagreb, Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a rare clinical entity, which first got its name in 2000 when it was used by Casey *et al.* (1). PRES was first described in 1996 by Hinchey *et al.* in a study of 15 patients. They used the term "reversible posterior leukoencephalopathy syndrome (RPLS)" which was characterized by clinical symptoms such as headache, confusion, disturbances of consciousness, visual impairment, and seizures. These symptoms correlated with the typical neuroimaging features consisting of posterior-predominant cortical or subcortical white matter oedema within the parietal and occipital lobes. It was the involvement of subcortical white matter that made them add the prefix "leuko" in the name which suggests only white matter involvement (2). However, imaging findings in the setting of PRES are not often exclusively confined to the white matter, and often extend to involve the overlying cerebral cortex, basal ganglia, brainstem, and cerebellum, which is why this name is not completely satisfactory (3). PRES in literature is also often referred to as "reversible posterior cerebral edema syndrome", "posterior leukoencephalopathy syndrome", "reversible occipital-parietal encephalopathy", "hypertensive encephalopathy", "hyperperfusion encephalopathy" and "brain capillary leak syndrome". While PRES most commonly manifests on imaging as cortical or subcortical oedema within the parietal and occipital lobes, it may also occur in an atypical fashion with the involvement of other regions such as the frontal lobe, temporal lobe, basal ganglia, thalamus, brainstem, or cerebellum, and even spinal cord without the involvement of the cerebral hemispheres (1,4,5,6).

Therefore, none of these names are completely satisfactory as the syndrome is not often restricted to either the white matter or the posterior regions of the brain, and it is not always reversible. PRES is potentially reversible and patient prognosis is often positive with timely recognition and removal of the inciting factors leading to PRES. However, death and permanent neurological damage have been reported in a small number of patients, as has the recurrence of PRES in 6% of the cases. Hence, in 2016 Kabre and Kamble proposed a new terminology "potentially reversible encephalopathy syndrome" (7).

PATHOPHYSIOLOGY

The precise pathophysiological mechanism underlying the development of PRES has yet to be fully clarified (8). There are two main proposed theories for the pathophysiology of PRES. The hypertensive and cerebral hyperperfusion theory describes severe arterial hypertension as the key factor for the development of PRES (9), proposing that the primary cause of vasogenic oedema is the loss of autoregulation in the posterior circulatory area of the cerebral vascular system due to large and sudden increases in blood pressure, which leads to cerebral hyperperfusion and consequential blood-brain barrier dysfunction, causing vascular leakage (10). The area of the central nervous system supplied by the posterior circulation show predilection for brain oedema, compared to the area supplied by anterior circulation, due to the lack of sympathetic tone of basilar artery vasculature (9). Likewise, the cortex is less prone to oedema, as it is structurally more tightly packed, unlike the white matter (11). This theory is based on the fact that hypertension is a common occurrence in patients with PRES, on reports of cerebral hyperperfusion in patients imaged with TcPPm-HMPAO single-photon emission computed tomography (SPECT), and on animal studies showing the development of cerebral hyperperfusion and vasogenic oedema with experimentally elevated blood pressure (12). However, the development of PRES in patients with normal or mildly increased blood pressure, as well as studies demonstrating cerebral hypoperfusion in patients with PRES, and lack of correlation with the degree of the severity of hypertension and brain oedema, point to the shortcomings of this theory (8).

A related vasoconstriction and cerebral hypoperfusion theory describes cerebral ischemia as a key factor in the pathophysiology of PRES. According to this theory, extreme hypertension results in focal vasoconstriction due to autoregulatory compensation, leading to reduced cerebral perfusion and local ischemia, which causes blood-brain barrier breakdown and the development of vasogenic oedema (13, 14). This sequence of events, leading to the development of PRES, was noticed in patients being treated with immunosuppressive agents such as cyclosporin A and tacrolimus (14). Even though cerebral infarction is an unusual occurrence in patients with PRES, there is a possibility that it develops due to microcirculation compression caused by vasogenic oedema. Some imaging studies that have used magnetic resonance (MR) perfusion have shown reduced brain perfusion in patients with PRES. This theory is also supported by the evidence of vasculopathy as demonstrated using catheter angiography in patients with vasoconstriction and hypoperfusion, as well as by the common occurrence of typical PRES imaging

features in watershed distribution. Nevertheless, it is considered that cerebral ischemia does not play a big part in the pathophysiology of PRES in most patients (15, 16).

The second major theory is the endothelial dysfunction theory, which proposes endothelial injury caused by various circulating endogenous or exogenous toxins as the primary cause of PRES. Circulating toxins cause endothelial injury which causes further release of vasoconstrictive and immunogenic agents, leading to vasoconstriction, increased vascular permeability, and the development of vasogenic oedema. According to this theory, the development of PRES is due to immune system activation that induces endothelial dysfunction suggesting that hypertension and vasoconstriction are not the primary causes in the pathophysiological mechanism of PRES. Cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), induce the expression of adhesion molecules which interact with circulating leukocytes and trigger the release of reactive oxygen species (ROS) and proteases, leading to endothelial injury and vascular leakage (17). These cytokines also trigger astrocytes to produce vascular endothelial growth factor (VEGF), which leads to the weakening of endothelial cell tight junctions and the breakdown of the blood-brain barrier. Additionally, VEGF activates the vesiculo-vacuolar organelle, thus creating the main way for the extravasation of fluids and macromolecules (18). Also, increased levels of leukocyte adhesion molecules have been registered in preeclampsia, solid organ transplantation, allogenic bone marrow transplantation, infection, sepsis, and shock (8). In their study, Marra *et al.* showed that increased levels of VEGF in patients with preeclampsia result in a fivefold increase in vascular permeability (17). Likewise, in one case of PRES following heart transplantation, a brain biopsy showed endothelial activation, T-cell trafficking, and endothelial VEGF expression (17, 19).

In patients with normal arterial blood pressure, cytotoxic medications may have a direct effect on vascular endothelium, causing endothelial dysfunction, and capillary leakage, leading to blood-brain barrier breakdown and axonal swelling, and subsequently vasogenic oedema (20).

Elevated levels of endothelial dysfunction markers, such as lactate dehydrogenase and abnormal red blood cell morphology, can be found in patients with preeclampsia, and they usually arise prior to the clinical syndrome. They also correlate better with the extent of cerebral oedema, than changes in blood pressure (21, 22). More specific markers of endothelial dysfunction seen in patients with preeclampsia include fibronectin, tissue plasminogen activator, thrombomodulin, endothelin-1, and von Willebrand factor (23, 24). These markers have also been registered in other states associated with PRES, such as chronic kidney failure, lupus nephritis, and hemolytic uremic syndrome (25). Although in patients with thrombotic thrombocytopenic purpura who developed PRES, hypertension and renal insufficiency usually occurred simultaneously, a case was reported in which these two complications were absent, suggesting endothelial dysfunction as the primary factor in the development of PRES (26, 27).

The theory of endothelial dysfunction is based on the fact that up to 30% of patients with PRES do not have elevated arterial blood pressure levels that are necessary for the breakdown of the autoregulation mechanism of the cerebral vasculature (28,29), and can also explain the development of PRES in patients who are going through chemotherapy or immunosuppressive therapy, and in systemic conditions characterized by endothelial damage and the absence of severe hypertension, such as sepsis, preeclampsia, and after bone marrow transplantation (30,31).

Another theory on the pathophysiology of PRES was recently published, which suggests arginine vasopressin (AVP) hypersecretion as a possible mechanism in the development of PRES. Numerous conditions associated with PRES, such as sepsis and eclampsia, have also been associated with AVP hypersecretion. In their study, Largeau *et al.* hypothesized that increased AVP secretion or AVP receptor density will lead to activation of vasopressin V1a with consequent cerebral vasoconstriction, endothelial dysfunction, and cerebral ischemia with resultant cytotoxic oedema, which may ultimately lead to increased endothelial permeability and subsequent vasogenic oedema. This theory is significant as it creates the possibility for pharmacological treatment of PRES by targeting the AVP pathway (32).

Although the pathophysiology of PRES is still a controversial topic and the exact pathophysiological mechanism remains unclear, blood-brain barrier dysfunction is generally accepted as the initial step for the formation of vasogenic oedema with predominantly affected posterior circulation of the central nervous system, regardless of whether the underlying cause is arterial hypertension or endothelial damage caused by circulating toxins. Still, it should also be kept in mind that the underlying cause may be a combination of interrelated processes, due to the heterogeneous nature of PRES (33).

ETIOLOGY

PRES is a rare syndrome, but the causes are numerous. The most common conditions associated with the development of PRES are moderate to severe hypertension, preeclampsia, eclampsia, the use of immunosuppressant and cytotoxic drugs most commonly in patients with hematopoietic malignancies, and in the setting of bone marrow, stem cell, or solid organ transplantation, infection with sepsis and shock, autoimmune disorders, and acute or chronic kidney disease that can ultimately lead to renal insufficiency (8, 34, 49). In their study, Fugate *et al.* found that hypertension was the causative factor in 61% of patients, cytotoxic drugs in 19%, sepsis in 7%, preeclampsia or eclampsia in 6%, and multiple organ failure in 1% of patients, while autoimmune disorders were present in 45% of patients (35).

Although some patients with PRES are normotensive at presentation, in most of them their blood pressure is higher compared to the initial value of blood pressure, while a minority of them are truly normotensive, and sometimes even hypotensive (1, 34). However, according to some studies, it also appears that PRES may be more common in patients with various comorbidities, such as systemic lupus erythematosus (SLE) (50,51,52), cryoglobulinemia (53), thrombotic thrombocytopenic purpura (TTP) (26), and hemolytic uremic syndrome (HUS) (54,55), and in patients on immunosuppressive and cytotoxic drugs, such as cyclosporine (52, 56), or cisplatin (20). They also noticed a higher incidence of renal failure in hypertensive patients with PRES, which may suggest a role for fluid overload, electrolyte disturbances, or uremia (57).

The development of PRES has also been described in patients who took immunosuppressive and immunomodulatory drugs as part of treatment for malignant or rheumatologic conditions and after transplantation of bone marrow, stem cells, and solid organs (35). These medications have a well-known neurotoxic effect, which has not been fully explained. PRES can develop in patients after several months of using these drugs, during the maintenance phase, which means that elevated or toxic levels of medications are not necessary for the development of PRES. Likewise, previous exposure to these medications does not appear to have a protective effect (25). One of the most common immunosuppressive agents associated with the development of PRES is cyclosporine. It is indicated after solid organ and bone marrow transplantation, and in the prevention of graft rejection after solid organ, allogenic bone marrow, and stem cell transplantation, and in the prevention of graft-versus-host disease (GVHD), but it is also extremely nephrotoxic and neurotoxic (56). Hypertension, hypomagnesemia, and hypocholesterolemia have been known to enhance the neurotoxic effect of cyclosporine, and in turn, cyclosporine may exacerbate hypertension by inhibiting nitric oxide production (58). Other common chemotherapeutic agents associated with the development of PRES include platinum-containing drugs, CHOP/R-CHOP regimens (cyclophosphamide, doxorubicin, vincristine, prednisone or prednisolone, rituximab), and gemcitabine (59,60). Apart from them, PRES can also occur with the use of other medications such as sirolimus (61), tacrolimus (62), interferon alpha, bevacizumab (63, 64), and tyrosine kinase inhibitors (pazopanib, sorafenib, sunitinib) (35).

Autoimmune disorders associated with the development of PRES include SLE, cryoglobulinemia, polyarteritis nodosa (PAN), TTP, granulomatosis with polyangiitis (GPA), inflammatory bowel diseases (Crohn's disease, ulcerative colitis), rheumatoid arthritis (RA), Sjörgen syndrome and neuromyelitis optica (35). High percentage of patients with PRES suffering from an autoimmune disorder supports the theory of endothelial dysfunction as a mechanism of PRES. However, it is still unclear whether the primary cause of PRES is the presence of one of these disorders, or if PRES is caused due to the use of medications for treatment of these disorders. Leroux *et al.* conducted a study on a group of 46 patients with SLE who developed PRES, but the role of SLE itself in the development of PRES was not clear, because 95% of patients already had arterial hypertension, 91% had reduced kidney function, 54% received immunosuppressive therapy, and 43% received intravenous steroids (65).

PRES was also described in patients with sepsis, and acute and chronic kidney disease (35, 66). In patients with SLE, renal dysfunction is a particularly important risk factor (66).

PRES can occur in any age group. Some cases of PRES have been described in the pediatric population. Although most cases of PRES in children have been described in oncology patients, especially those after stem cell transplantation (67, 65), a study by Gupta *et al.* showed that most likely kidney disease is the most common cause of PRES in the pediatric population (68).

IMAGING

PRES is typically presented on neuroimaging findings as posterior-predominant bilateral and sym-

metric vasogenic oedema involving subcortical white matter, with a common parieto-occipital lesion distribution pattern (34). However, the paramedian parts of the occipital lobe are usually not affected, which helps distinguish PRES from bilateral posterior cerebral infarctions (35). In PRES, T2-weighted and FLAIR sequences on MRI often show focal or confluent areas of increased signal in the posterior-predominant subcortical white matter (36). In addition to the posterior parts of the hemispheres, the frontal lobes (up to 68%), especially the upper frontal gyrus, are also often affected by the oedema. Although they are uncommon, isolated posterior fossa lesions are increasingly described (25,37). In a small number of patients, temporal lobe oedema has also been described (37).

In addition to the typical posterior-predominant pattern involving parietal-occipital regions, other patterns of lesion distribution can be observed on MRI and have been described by Bartynski and Boardman in their study (37). In Fig. 1 we show a less common pattern of central PRES due to hypertension, which resolved completely after therapy. Likewise, the use of FLAIR sequences on MRI improved sensitivity and enabled detection of peripheral and cortical lesions, which turned out to be much more common (25). Therefore, four other patterns of oedema distribution in PRES have been described: holohemispheric watershed pattern, superior frontal sulcus pattern, a dominant parietal-occipital pattern, and partial or asymmetric expression of these primary patterns. In the holohemispheric watershed pattern, vasogenic oedema involves the frontal, parietal and occipital lobes. Superior frontal sulcus pattern is characterized by the prominent involvement of the frontal lobe with varying parietal-occipital involvement, while the partial or asymmetric expression of these primary patterns refers to the bilateral or unilateral lack of signal in parietal-occipital regions (25, 37).

PRES may present with atypical imaging findings, in terms of regions involved or different types of lesions not related to vasogenic oedema that can cause further complications such as cerebral hemorrhage, diffusion restriction, or contrast enhancement/imbibition (38,39). Atypical regions that may be involved include the brainstem, cerebellum, basal ganglia, thalamus, corpus callosum, and the spinal cord. A study by McKinney *et al.* conducted on 124 patients with PRES, showed the involvement of the brainstem and basal ganglia without the presence of cortical or subcortical oedema in as many as 4% of patients (40). They also conducted an additional study consisting of 76 patients with PRES, which showed involvement of thalamus involvement in 30,3% of patients, cerebellum in 34,2% of patients, brainstem in 18,4%, and basal ganglia in 11,8% with unilateral involvement in 2,6% of patients (4). Liman *et al.* studied a cohort of 96 patients diagnosed with PRES, and in more than 50% of patients found infratentorial involvement, predominantly in the cerebellum and pons, whilst around 25% of patients showed basal ganglia and thalamus involvement (5). In their study, Kastrup *et al*. described the involvement of the basal ganglia in 1,6% of patients, and of the cerebellum in 6,5% of patients (6). The involvement of the spinal cord in patients with PRES is exceptional, and only a few cases have been described, with confluent and expansive areas of increased signal found in the central part of the spinal cord as shown on the T2-weighted sequence on MRI (41).

PRES may be complicated by cerebral hemorrhage. Several patterns of cerebral hemorrhage have been described, such as large hematomas causing compression of surrounding structures, subarachnoid hemorrhage (SAH), or multiple focal microhemorrhages (<5 mm) (42). The overall rate of cerebral hemorrhage in patients with PRES ranges from 15% to 65%, with the higher percentage reflecting the greater number of reported cases (43). The exact mechanism of cerebral hemorrhage in PRES is still unknown. In a study conducted by Hefzy *et al.* on a group of 151 patients, 15% of cases of cerebral hemorrhage were recorded, with the incidence being highest in cases of immunosuppression, more commonly in patients following bone marrow transplantation than in solid organ transplantation. No difference in the incidence of cerebral hemorrhage was observed in patients with normal, slightly elevated, or extremely elevated blood pressure (38). McKinney *et al.* observed that the proportion of patients who developed cerebral hemorrhage was much higher (64,5%), due to the increased use of SWI (susceptibility-weighted imaging), as it is more sensitive in the detection of hemorrhage (44).

In addition, PRES may be complicated by the development of cytotoxic oedema as indicated by diffusion restriction. Areas of reduced diffusion are usually small, punctate, and are located within confluent lesions of vasogenic oedema. Since vasogenic oedema is a characteristic imaging finding in PRES, MRI by FLAIR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) help us in differentiating types of oedema. Isointense or hyperintense signal on DWI and hyperintense signal on ADC sequence are a feature of

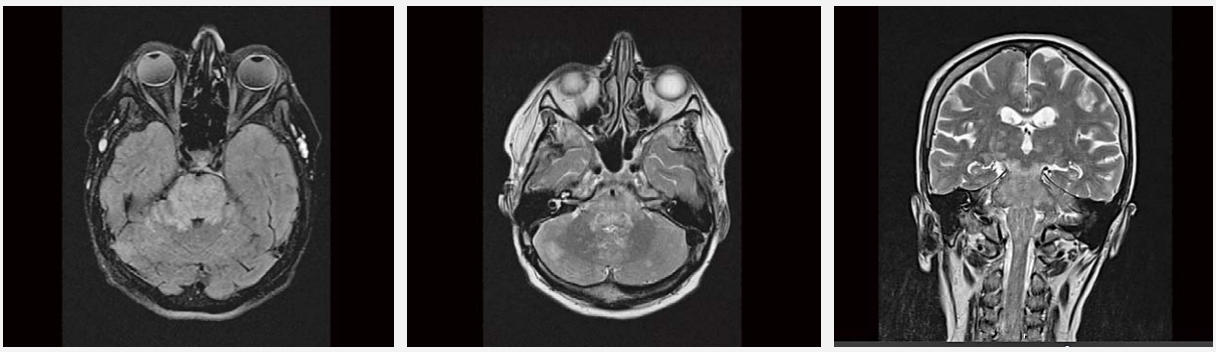


Fig. 1. *Brain MRI of a 59-year-old hypertensive female patient with renal impairment showing typical hyperintense changes in brain stem and in cerebellar both hemispheres on T2/FLAIR sequences.*

vasogenic oedema, while hyperintense signal on DWI and hypointense signal on ADC sequence are characteristics of cytotoxic oedema (45). According to data from previously published studies, approximately 10% - 33% of patients with PRES develop cytotoxic oedema (46,47), which is thought to be a consequence of late treatment, resulting in persistent hyperperfusion and vessel injury caused by the mass effect of vasogenic oedema on the surrounding tissue, which ultimately leads to ischemia and brain infarction (4).

Superficial leptomeningeal enhancement is the most common pattern seen on MRI. Additionally, a nodular and, in a third of patients, a combined leptomeningeal and gyral cortical pattern can be described too (39,41).

MR angiography often shows vasculopathic changes in patients with PRES. In their study, Bartynski *et al.* discovered evidence of diffuse or focal vasoconstriction in 87% of patients (48).

TREATMENT OPTIONS

Treatment of PRES is aimed at removing the primary condition leading to PRES and includes symptomatic treatment. In cases of hypertension, treatment is aimed at gradual and careful blood pressure lowering (69), while in cases of preeclampsia/eclampsia, it is aimed at the timely delivery of the baby as well as careful blood pressure lowering (70). In cases of PRES induced by cytotoxic or immunosuppressive agents, prompt removal of the drug is usually recommended and leads to clinical and radiological improvement (69,71). Seizures are treated with parenteral benzodiazepines (diazepam) (69), while magnesium sulphate is used for seizure prophylaxis in the setting of preeclampsia/eclampsia (70). It is important to promptly recognize and treat conditions that are known to contribute to the development and poor prognosis in patients with PRES, such as electrolyte disturbances, volume overload, uremia, and sepsis. Hypomagnesemia is a common finding in patients with PRES, and it is believed that magnesium supplementation may be useful in the treatment of PRES (69, 72).

CONCLUSION

PRES is a rare clinical and radiographic syndrome with numerous causes and characteristic neurological symptoms and imaging findings, although it may present with atypical imaging findings too. The exact pathophysiological mechanism has yet to be fully clarified and remains a controversial topic. PRES is usually reversible. If the cause is recognized and removed, the prognosis is generally good, and most patients recover within a few weeks. Unfortunately, a certain number of patients die or are left with permanent neurologic deficits.

Acknowledgment of the source(s) of support:

I would like to extend my deepest gratitude and appreciation to my mentor Professor Zdravka Poljaković-Skurić, MD, PhD for her valubale advice, support, and extensive knowledge that helped me write this work.

REFERENCES

1. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. AJNR Am J Neuroradiol. 2000 Aug; 21(7):1199-206.
2. Hinchey J, Chaves C, Appignani B, *et al.* A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996 Feb 22; 334(8):494-500.

3. Saad AF, Chaudhari R, Wintermark M. Imaging of Atypical and Complicated Posterior Reversible Encephalopathy Syndrome. Front Neurol. 2019 Sep 4;10:964. doi: 10.3389/fneur.2019.00964. PMID: 31551919; PMCID: PMC6738024

4. McKinney AM, Short J, Truwit CL, *et al.* Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol. 2007 Oct;189(4):904-12. doi: 10.2214/AJR.07.2024. PMID: 17885064.

5. Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study. J Neurol. 2012 Jan;259(1):155-64. doi: 10.1007/s00415-011-6152-4. Epub 2011 Jun 30. PMID: 21717193.

6. Kastrup O, Schlamann M, Moenninghoff C, Forsting M, Goericke S. Posterior Reversible Encephalopathy Syndrome: The Spectrum of MR Imaging Patterns. Clin Neuroradiol. 2015 Jun; 25(2):161-71. doi: 10.1007/s00062-014-0293-7. Epub 2014 Feb 20. PMID: 24554281.

7. Kabre RS and Kamble KM. Gemcitabine and Cisplatin induced posterior reversible encephalopathy syndrome: A case report with review of literature J Res Pharm Pract. 2016 Oct-Dec; 5(4): 297–300

8. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. AJNR Am J Neuroradiol. 2008 Jun;29(6):1043-9. doi: 10.3174/ajnr.A0929. Epub 2008 Apr 10. PMID: 18403560; PMCID: PMC8118813.

9. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015 Sep; 14(9):914-925. doi: 10.1016/S1474-4422(15)00111-8. Epub 2015 Jul 13. Erratum in: Lancet Neurol. 2015 Sep;14(9):874. PMID: 26184985.

10. Paulson OB, Waldemar G, Schmidt JF, Strandgaard S. Cerebral circulation under normal and pathologic conditions. Am J Cardiol. 1989 Feb 2;63(6):2C-5C. doi: 10.1016/0002-9149(89)90396-2. PMID: 2643850.

11. Kalimo H, Fredriksson K, Nordborg C, Auer RN, Olsson Y, Johansson B. The spread of brain oedema in hypertensive brain injury. Med Biol. 1986;64(2-3):133-7. PMID: 3747621.

12. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood-brain barrier. Circ Res. 1976 Jul;39(1):33-41. doi: 10.1161/01.res.39.1.33. PMID: 1277403.

13. Toole JF. Lacunar syndromes and hypertensive encephalopathy. In: Toole JF, editor. Cerebrovascular Disorders. 5th ed. New York, NY: Raven; (1999). p. 342–55.

14. Bartynski WS, Zeigler Z, Spearman MP, Lin L, Shadduck RK, Lister J. Etiology of cortical and white matter lesions in cyclosporin-A and FK-506 neurotoxicity. AJNR Am J Neuroradiol. 2001 Nov-Dec;22(10):1901-14. PMID: 11733324; PMCID: PMC7973826.

15. Brubaker LM, Smith JK, Lee YZ, Lin W, Castillo M. Hemodynamic and permeability changes in posterior reversible encephalopathy syndrome measured by dynamic susceptibility perfusion-weighted MR imaging. AJNR Am J Neuroradiol. 2005 Apr;26(4):825-30. PMID: 15814928; PMCID: PMC7977102.

16. Engelter ST, Petrella JR, Alberts MJ, Provenzale JM. Assessment of cerebral microcirculation in a patient with hypertensive encephalopathy using MR perfusion imaging. AJR Am J Roentgenol. 1999 Dec;173(6):1491-3. doi: 10.2214/ajr.173.6.10584788. PMID: 10584788.

17. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. Med Hypotheses. 2014 May;82(5):619-22. doi: 10.1016/j.mehy.2014.02.022. Epub 2014 Mar 1. PMID: 24613735.

18. Park SJ, Pai KS, Kim JH, Shin JI. Could increased vascular endothelial growth factor induced by interleukin 17 be the cause of posterior reversible encephalopathy syndrome in systemic lupus erythematosus? J Rheumatol. 2012 Apr;39(4):870; author reply 871. doi: 10.3899/jrheum.111124. PMID: 22467951.

19. Tetsuka S, Ogawa T. Posterior reversible encephalopathy syndrome: A review with emphasis on neuroimaging characteristics. J Neurol Sci. 2019 Sep 15;404:72-79. doi: 10.1016/j.jns.2019.07.018. Epub 2019 Jul 17. PMID: 31349066.

20. Ito Y, Arahata Y, Goto Y, *et al.* Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. AJNR Am J Neuroradiol. 1998 Mar;19(3):415-7. PMID: 9541291; PMCID: PMC8338246.

21. Schwartz RB, Feske SK, Polak JF, *et al.* Preeclampsia-eclampsia: clinical and neuroradiographic correlates and insights into the patho-

genesis of hypertensive encephalopathy. Radiology. 2000 Nov;217(2):371-6. doi: 10.1148/radiology.217.2.r00nv44371. PMID: 11058630.

22. Easton JD. Severe preeclampsia/eclampsia: hypertensive encephalopathy of pregnancy? Cerebrovasc Dis. 1998 Jan-Feb;8(1):53-8. doi: 10.1159/000015818. PMID: 9645984.

23. Rodgers GM, Taylor RN, Roberts JM. Preeclampsia is associated with a serum factor cytotoxic to human endothelial cells. Am J Obstet Gynecol. 1988 Oct;159(4):908-14. doi: 10.1016/s0002-9378(88)80169-8. PMID: 3177546.

24. Blann AD, Taberner DA. A reliable marker of endothelial cell dysfunction: does it exist? Br J Haematol. 1995 Jun;90(2):244-8. doi: 10.1111/j.1365-2141.1995.tb05143.x. PMID: 7540851.

25. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol. 2002 Jun-Jul;23(6):1038-48. PMID: 12063238; PMCID: PMC7976914.

26. Burrus TM, Mandrekar J, Wijdicks EF, Rabinstein AA. Renal failure and posterior reversible encephalopathy syndrome in patients with thrombotic thrombocytopenic purpura. Arch Neurol. 2010 Jul;67(7):831-4. doi: 10.1001/archneurol.2010.119. PMID: 20625089.

27. Hawley JS, Ney JP, Swanberg MM. Thrombotic thrombocytopenic purpura-induced posterior leukoencephalopathy in a patient without significant renal or hypertensive complications. J Postgrad Med. 2004 Jul-Sep;50(3):197-9. PMID: 15377805.

28. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017 Aug;264(8):1608-1616. doi: 10.1007/s00415-016-8377-8. Epub 2017 Jan 4. PMID: 28054130; PMCID: PMC5533845.

29. Feske SK. Posterior reversible encephalopathy syndrome: a review. Semin Neurol. 2011 Apr;31(2):202-15. doi: 10.1055/s-0031-1277990. Epub 2011 May 17. PMID: 21590625.

30. Bartynski WS, Boardman JF, Zeigler ZR, Shadduck RK, Lister J. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. AJNR Am J Neuroradiol. 2006 Nov-Dec;27(10):2179-90. PMID: 17110690; PMCID: PMC7977225.

31. Mayama M, Uno K, Tano S, *et al.* Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms. Am J Obstet Gynecol. 2016 Aug;215(2):239.e1-5. doi: 10.1016/j.ajog.2016.02.039. Epub 2016 Feb 20. PMID: 26902987.

32. Largeau B, Le Tilly O, Sautenet B, Salmon Gandonnière C, Barin-Le Guellec C, Ehrmann S. Arginine Vasopressin and Posterior Reversible Encephalopathy Syndrome Pathophysiology: the Missing Link? Mol Neurobiol. 2019 Oct;56(10):6792-6806. doi: 10.1007/s12035-019-1553-y. Epub 2019 Mar 28. PMID: 30924075.

33. Anderson RC, Patel V, Sheikh-Bahaei N, *et al.* Posterior Reversible Encephalopathy Syndrome (PRES): Pathophysiology and Neuro-Imaging. Front Neurol. 2020 Jun 16;11:463. doi: 10.3389/fneur.2020.00463. PMID: 32612567; PMCID: PMC7308488.

34. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol. 2008 Jun;29(6):1036-42. doi: 10.3174/ajnr.A0928. Epub 2008 Mar 20. PMID: 18356474; PMCID: PMC8118828.

35. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc. 2010 May;85(5):427-32. doi: 10.4065/mcp.2009.0590. PMID: 20435835; PMCID: PMC2861971.

36. Lamy C, Oppenheim C, Méder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. J Neuroimaging. 2004 Apr;14(2):89-96. PMID: 15095552.

37. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2007 Aug;28(7):1320-7. doi: 10.3174/ajnr.A0549. PMID: 17698535; PMCID: PMC7977645.

38. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. AJNR Am J Neuroradiol. 2009 Aug;30(7):1371-9. doi: 10.3174/ajnr.A1588. Epub 2009 Apr 22. PMID: 19386731; PMCID: PMC7051550.

39. Karia SJ, Rykken JB, McKinney ZJ, Zhang L, McKinney AM. Utility and Significance of Gadolinium-Based Contrast Enhancement in Posterior Reversible Encephalopathy Syndrome. AJNR Am J Neuroradiol. 2016 Mar;37(3):415-22. doi: 10.3174/ajnr.A4563. Epub 2015 Nov 12. PMID: 26564441; PMCID: PMC5584787.

40. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy

syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema. AJR Am J Roentgenol. 2013 Sep;201 (3):631-8. doi: 10.2214/AJR.12.9677. PMID: 239 71457.

41. Ollivier M, Bertrand A, Clarençon F, *et al.* Neuroimaging features in posterior reversible encephalopathy syndrome: A pictorial review. J Neurol Sci. 2017 Feb 15;373:188-200. doi: 10. 1016/j.jns.2016.12.007. Epub 2016 Dec 8. PMID: 28131186.
42. Sharma A, Whitesell RT, Moran KJ. Imaging pattern of intracranial hemorrhage in the setting of posterior reversible encephalopathy syndrome. Neuroradiology. 2010 Oct;52(10):855-63. doi: 10.1007/s00234-009-0632-6. Epub 2009 Dec 3. PMID: 19956935.
43. Brady E, Parikh NS, Navi BB, Gupta A, Schweitzer AD. The imaging spectrum of posterior reversible encephalopathy syndrome: A pictorial review. Clin Imaging. 2018 Jan-Feb;47:80-89. doi: 10.1016/j.clinimag.2017.08.008. Epub 2017 Aug 30. PMID: 28910681.
44. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. AJNR Am J Neuroradiol. 2012 May;33(5):896-903. doi: 10.3174/ ajnr.A2886. Epub 2012 Jan 12. PMID: 22241378; PMCID: PMC7968802.
45. Wagih A, Mohsen L, Rayan MM, Hasan MM, Al-Sherif AH. Posterior Reversible Encephalopathy Syndrome (PRES): Restricted Diffusion does not Necessarily Mean Irreversibility. Pol J Radiol. 2015 Apr 25;80:210-6. doi: 10.12659/ PJR.893460. PMID: 25960819; PMCID: PMC 4418207.
46. Gao B, Yu BX, Li RS, *et al.* Cytotoxic Edema in Posterior Reversible Encephalopathy Syndrome: Correlation of MRI Features with Serum Albumin Levels. AJNR Am J Neuroradiol. 2015 Oct; 36(10):1884-9. doi: 10.3174/ajnr.A4379. Epub 2015 Jul 2. PMID: 26138140; PMCID: PMC 7965038.
47. Zeeman GG, Fleckenstein JL, Twickler DM, Cunningham FG. Cerebral infarction in eclampsia. Am J Obstet Gynecol. 2004 Mar;190(3): 714-20. doi: 10.1016/j.ajog.2003.09.015. PMID: 15042004.
48. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2008 Mar;29(3):447-55. doi: 10.3174/ajnr.A0839. Epub 2007 Dec 13. PMID: 18079186; PMCID: PMC8118858.
49. Lamy C, Oppenheim C, Mas JL. Posterior reversible encephalopathy syndrome. Handb Clin Neurol. 2014;121:1687-701. doi: 10.1016/B978-0-7020-4088-7.00109-7. PMID: 24365441.
50. Leroux G, Sellam J, Costedoat-Chalumeau N, *et al.* Posterior reversible encephalopathy syndrome during systemic lupus erythematosus: four new cases and review of the literature. Lupus. 2008 Feb;17(2):139-47. doi: 10.1177/0961 203307085405. PMID: 18250139.
51. Mak A, Chan BP, Yeh IB, *et al.* Neuropsychiatric lupus and reversible posterior leucoencephalopathy syndrome: a challenging clinical dilemma. Rheumatology (Oxford). 2008 Mar;47(3):256-62. doi: 10.1093/rheumatology/kem319. Epub 2007 Dec 15. PMID: 18084001.
52. Schwartz RB, Bravo SM, Klufas RA, *et al.* Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. AJR Am J Roentgenol. 1995 Sep; 165(3):627-31. doi: 10.2214/ajr.165.3.7645483. PMID: 7645483.
53. Hodson AK, Doughty RA, Norman ME. Acute encephalopathy, streptococcal infection, and cryoglobulinemia. Arch Neurol. 1978 Jan;35(1): 43-4. doi: 10.1001/archneur.1978.00500250047 011. PMID: 619873.
54. Schwartz RB, Mulkern RV, Gudbjartsson H, Jolesz F. Diffusion-weighted MR imaging in hypertensive encephalopathy: clues to pathogenesis. AJNR Am J Neuroradiol. 1998 May;19(5):859-62. PMID: 9613500; PMCID: PMC8337583.
55. Magnano MD, Bush TM, Herrera I, Altman RD. Reversible posterior leukoencephalopathy in patients with systemic lupus erythematosus. Semin Arthritis Rheum. 2006 Jun;35(6):396-402. doi: 10.1016/j.semarthrit.2006.01.002. PMID: 16765717.
56. Serkova NJ, Christians U, Benet LZ. Biochemical mechanisms of cyclosporine neurotoxicity. Mol Interv. 2004 Apr;4(2):97-107. doi: 10.1124/mi. 4.2.7. PMID: 15087483.
57. Dinsdale HB. Hypertensive encephalopathy. Neurol Clin. 1983 Feb;1(1):3-16. PMID: 6687306.
58. Kou R, Greif D, Michel T. Dephosphorylation of endothelial nitric-oxide synthase by vascular endothelial growth factor. Implications for the vascular responses to cyclosporin A. J Biol Chem. 2002 Aug 16;277(33):29669-73. doi: 10.1074/jbc. M204519200. Epub 2002 Jun 5. PMID: 12050171.
59. How J, Blattner M, Fowler S, Wang-Gillam A, Schindler SE. Chemotherapy-associated Posterior Reversible Encephalopathy Syndrome: A

Case Report and Review of the Literature. Neurologist. 2016 Nov;21(6):112-117. doi: 10.1097/NRL.0000000000000105. PMID: 27801773; PMCID: PMC8260039.

60. Rajasekhar A, George TJ Jr. Gemcitabine-induced reversible posterior leukoencephalopathy syndrome: a case report and review of the literature. Oncologist. 2007 Nov;12(11):1332-5. doi: 10.1634/theoncologist.12-11-1332. PMID: 18055853.

61. Bodkin CL, Eidelman BH. Sirolimus-induced posterior reversible encephalopathy. Neurology. 2007 Jun 5;68(23):2039-40. doi: 10.1212/01.wnl.0000264428.76387.87. PMID: 17548556.

62. Junna MR, Rabinstein AA. Tacrolimus induced leukoencephalopathy presenting with status epilepticus and prolonged coma. J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1410-1. doi: 10.1136/jnnp.2007.121806. PMID: 18024699; PMCID: PMC2095620.

63. Allen JA, Adlakha A, Bergethon PR. Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Arch Neurol. 2006 Oct;63(10):1475-8. doi: 10.1001/archneur.63.10.1475. PMID: 17030665.

64. Seet RC, Rabinstein AA. Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. QJM. 2012 Jan;105(1):69-75. doi: 10.1093/qjmed/hcr139. Epub 2011 Aug 24. PMID: 21865314.

65. Kim SJ, Im SA, Lee JW, *et al.* Predisposing factors of posterior reversible encephalopathy syndrome in acute childhood leukemia. Pediatr Neurol. 2012 Dec;47(6):436-42. doi: 10.1016/j.pediatrneurol.2012.07.011. PMID: 23127265.

66. Lai CC, Chen WS, Chang YS, *et al.* Clinical features and outcomes of posterior reversible encephalopathy syndrome in patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2013 Nov;65(11):1766-74. doi: 10.1002/acr.22047. PMID: 23687067.

67. Khan SJ, Arshad AA, Fayyaz MB, Ud Din Mirza I. Posterior Reversible Encephalopathy Syndrome in Pediatric Cancer: Clinical and Radiologic Findings. J Glob Oncol. 2018 Sep;4:1-8. doi: 10.1200/JGO.17.00089. Epub 2017 Dec 4. PMID: 30241146; PMCID: PMC6181184.

68. Gupta V, Bhatia V, Khandelwal N, Singh P, Singhi P. Imaging Findings in Pediatric Posterior Reversible Encephalopathy Syndrome (PRES): 5 Years of Experience From a Tertiary Care Center in India. J Child Neurol. 2016 Aug;31(9):1166-73. doi: 10.1177/0883073816643409. Epub 2016 Apr 12. PMID: 27071468.

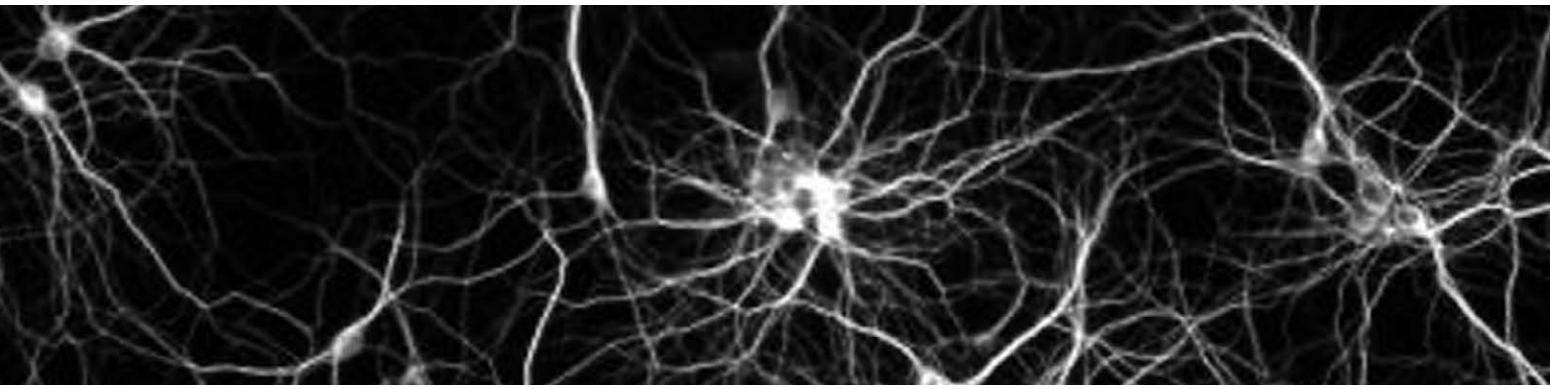
69. Neill, TA. Reversible posterior leukoencephalopathy syndrome. U: UpToDate, Post TW ur. UpToDate [Internet]. Waltham, MA: UpToDate; 2020 [pristupljeno 20.5.2022.] Dostupno na: http://www.uptodate.com

70. Cozzolino M, Bianchi C, Mariani G, Marchi L, Fambrini M, Mecacci F. Therapy and differential diagnosis of posterior reversible encephalopathy syndrome (PRES) during pregnancy and postpartum. Arch Gynecol Obstet. 2015 Dec;292(6):1217-23. doi: 10.1007/s00404-015-3800-4. Epub 2015 Jun 30. PMID: 26122264.

71. Masetti R, Cordelli DM, Zama D, *et al.* PRES in Children Undergoing Hematopoietic Stem Cell or Solid Organ Transplantation. Pediatrics. 2015 May;135(5):890-901. doi: 10.1542/peds.2014-2325. PMID: 25917987.

72. Almoussa M, Goertzen A, Brauckmann S, Fauser B, Zimmermann CW. Posterior Reversible Encephalopathy Syndrome due to Hypomagnesemia: A Case Report and Literature Review. Case Rep Med. 2018 Nov 29;2018:1980638. doi: 10.1155/2018/1980638. PMID: 30631367; PMCID: PMC6304829.

Address for correspondence: Zdravka Poljaković Skurić; E-mail: zdravka.po@gmail.com



Bilateral facial palsy and left abducens palsy in a patient with neuroborreliosis

Paula Božić[1], Romana Perković[2], Nataša Klepac[2], Fran Borovečki[2]

ABSTRACT – *Objectives: Borrelia burgdorferi* (BB) is causing Lyme disease (LD) which acutely manifests as erythema migrans (EM). If the infection is unrecognized and untreated it can progress to carditis, arthritis, or neurological disorders presented as meningitis, encephalitis, or cranial nerve palsies (CNPs). Most frequently affected are seventh and sixth cranial nerves (CNs) individually. *Case description:* In this case report we present a patient with sudden onset of bilateral peripheral facial palsy and left side abducens palsy who was hospitalised in the Department of Neurology, University Hospital Centre Zagreb. Results of wide diagnostics have shown polyclonal hypergammaglobulinemia and positive serology on BB. The patient was treated with ceftriaxone and acyclovir which resulted in improved neurological status. *Results:* Based on clinical presentation, positive serology on BB and good response to ceftriaxone treatment working, diagnosis of neuroborreliosis was confirmed. *Conclusion:* Simultaneous bilateral facial palsy and unilateral abducens palsy without EM is a rare manifestation of LD. Polyclonal hypergammaglobulinemia is proven to occur in acute infectious diseases but the specific relation between the condition and BB infection has not yet been investigated. Early diagnosis and treatment of LD are of immense importance because they prevent dissemination of infection and complications.

Keywords: abducens nerve palsy, *Borrelia burgdorferi,* neuroborreliosis, facial palsy, Lyme disease

OBJECTIVES

Lyme borreliosis or Lyme disease (LD) is a zoonosis affecting multiple organ systems (1). Spirochete *Borrelia burgdorferi* (BB) causes the infection and is transmitted through the bite of the tick (1, 2). Clinical manifestations are grouped into three stages: early localized stage, early disseminated stage, and late disseminated stage (3). The most frequent manifestation of LD is erythema migrans (EM) (89%) (1). If EM is unrecognised and untreated, 10%-15% of infections will progress to neuroborreliosis (3). The most common manifestation of acute Lyme neuroborreliosis in adults in Europe is meningoradiculoneuritis, also known as Garin-Bujadoux-

[1] Special Hospital for Medical Rehabilitation Varaždinske Toplice, Varaždinske Toplice, Croatia

[2] Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia

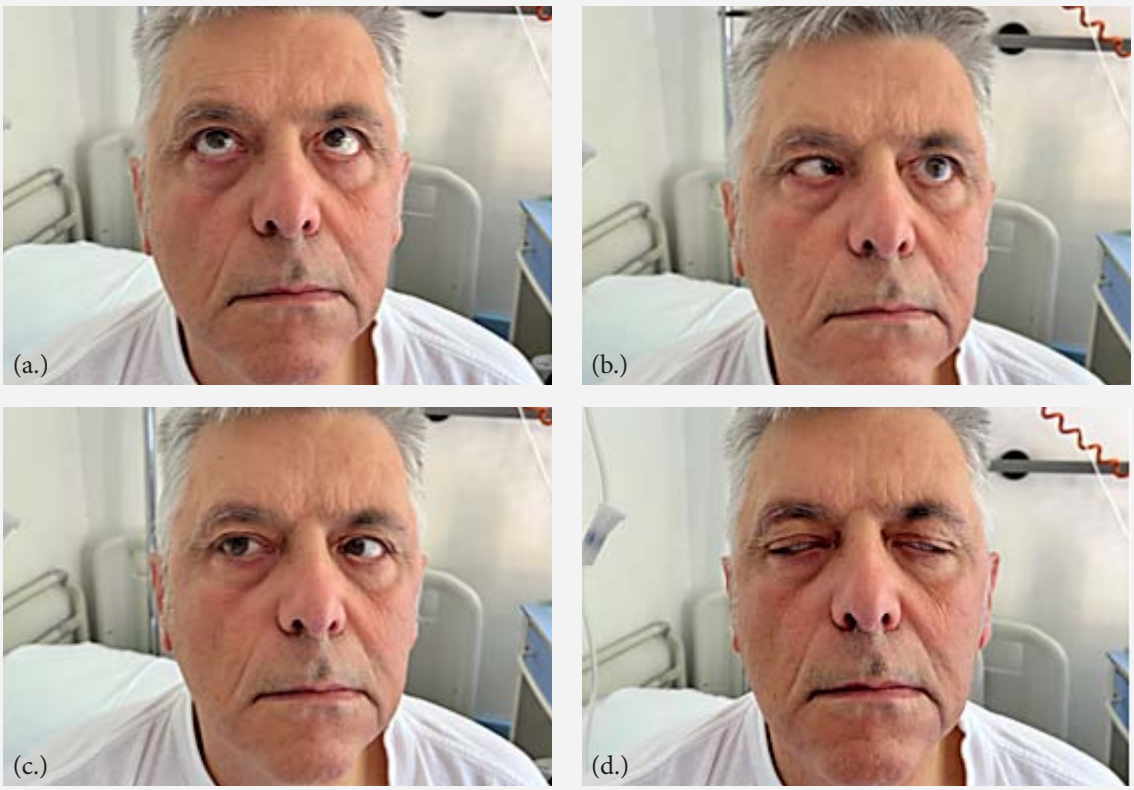


Fig. 1. *Photos taken during the neurological examination of CN innervation while the patient was hospitalised at the Department of Neurology, University Hospital Centre Zagreb: (a.) left abducens palsy presented as slightly adducted left eye when the patient is asked to look up due to tonic action of the medial rectus muscle; (b.) left abducens palsy presented as the inability to abduct left eyeball when looking left; (c.) presentation of eyeballs position when the patient is asked to look right; (d.) bilateral facial palsy presented as the inability to close both eyes and bilateral lowered mouth angle.*

Bannwarth syndrome, and the predominant symptom in about 60% of them is cranial nerve palsy (CNP) (1). The seventh cranial nerve (CN) is affected in 80% of cases and in about 30% of them it is bilateral (5). Other CN deficit is rarely described in the available literature. The second most often damaged nerve is the abducens nerve, occurring in about 5% of patients with Lyme neuroborreliosis (5). In this case report we present a 66-year-old man with an acute onset of neuroborreliosis symptoms and rare clinical manifestation of bilateral facial palsy and left side abducens palsy.

CASE DESCRIPTION

A 66-year-old patient was examined in the emergency room (ER) because of double vision in all directions and left abducens palsy. Besides double vision, he reported bilateral oropharyngeal tingling, headache, difficulty speaking, and lowered left mouth angle. The patient negated nausea, vomiting, fever, and allergies. A week and a half before the onset of symptoms, he was bitten by the thick. The patient did not notice erythema on the thick bite side. In neurological status, he was dysarthric, had left abducens palsy with double vision in all directions, and no nystagmus (Figure 1a-b), bilateral facial palsy (Figure 1d), and his tongue was left positioned in protrusion. From other diseases, he has had inguinal hernia surgery in 1996.

In ER standard laboratory tests, electrocardiogram, computed tomography (CT) of the brain with angiography of the head and neck vessels, polymerase chain reaction (PCR) for COVID-19, and cerebrospinal fluid (CSF) analysis were done. The results of all tests were without deviation from normal. The ophthalmologist examined the patient and did not find ophthalmological reasons for the patient's symptoms. He underwent carotid and vertebral ultrasound imaging with no findings of arterial stenosis. The patient was cardiopulmonary compensated, afebrile, and eupnoeic with blood pressure 140/80 mmHg and was hospitalized.

The literature describes a wide range of causes and differential diagnoses that are linked to cranial neuropathies. Some of them were considered in

Table 1. *Results of serology testing for BB in serum interpreted as Lyme borreliosis of undefined duration. Arbitrary units per millilitre (AU/ml).*

Search	Finding	Result	Unit	Method	Referent range
B. burgdorferi IgM	POSITIVE	>=190	AU/ml	CLIA	Pos. > 22 Neg. < 18
B. burgdorferi IgG	POSITIVE	186.9	AU/ml	CLIA	Pos. > 15 Neg. <10
B. burgdorferi IgM WB	POSITIVE			WB	Neg.
B. burgdorferi IgG WB	POSITIVE			WB	Neg.

Table 2. *Results of serology testing for BB in CSF. Arbitrary units per millilitre (AU/ml).*

Search	Finding	Result	Unit	Method	Referent range
B. burgdorferi IgM	negative			CLIA	Pos. > 3.5 Neg. < 2.5
B. burgdorferi IgG	REACTIVE	38.3	AU/ml	CLIA	Pos. > 5.5 Neg. < 4.5
Neuroborreliosis IgM	negative			EIA	Pos. > 0.3
Neuroborreliosis IgG	negative			EIA	Pos. > 0.3

this particular case: inflammatory and infectious (BB, *Treponema pallidum* (TP), *Varicella-zoster* virus (VZV), *Herpes simplex* virus (HSV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), *Mycobacterium tuberculosis* (TB), Toxoplasma gondii (TG)), autoimmune diseases (Guillain-Barré syndrome, multiple sclerosis, neurosarcoidosis, autoimmune encephalitis), stroke, tumor, head trauma, and anomalies of blood vessels. Therefore, a wide range of targeted neurological tests were done immediately upon hospitalisation. Magnetic resonance imaging (MRI) of the brain with contrast did not show pathological processes. Electroneurography of the upper and lower extremities did not show signs of polyneuropathy. Besides standard laboratory tests (haematology, biochemistry, and urine analysis), special biochemistry (proteins, IgG, IgA, IgM), electrophoresis of proteins in serum, coagulation tests, a broad spectrum of immunological markers including panel of antibodies for autoimmune encephalitis, proteins and specific proteins in serum (alfa-1-antitrypsin, ceruloplasmin, ferritin, haptoglobin, beta-2- microglobulin) and tumor markers values (AFP, CEA, CA19-9, PSA, NSE and CYFRA) were measured. Vitamin B12, folic acid, copper in serum and in 24-hour urine native and stimulated with penicillamine, iron, and UIBC were measured.

All laboratory findings were normal with the exception of polyclonal hypergammaglobulinemia which raises suspicion of autoimmune disease or infection. Immunology, Gastroenterology, and Haematology specialists were consulted, and further diagnostics were suggested. CT of the thorax, abdomen, and pelvis did not show any abnormalities.

Serum and CSF were tested for CMV, EBV, TG, VZV, HSV 1, and HSV 2. Methods that were used are enzyme-linked fluorescence assay (ELFA) and enzyme-linked immunosorbent assay (ELISA). Also, PCR for HSV and Interferon Gamma Release Assay (IGRA) known as QuantiFERON-TB-Gold ELISA for detection of TB and serologic tests for Syphilis (Venereal Disease Research Laboratory / Rapid Plasma Reagin (VDRL/RPR), Treponema pallidum hemagglutination (TPHA) test and IgM and IgG- Fluorescent Treponemal Antibody Absorption (FTA-ABS)). Chemiluminescence immunoassay (CLIA), Western blot (WB), and Enzyme immunoassay (EIA) were used to detect BB in serum and CSF. Positive serology results of BB were the key for making a final diagnosis which was neuroborreliosis with reactive polyclonal hypergammaglobulinemia (Table 1. and Table 2.).

The patient was treated with 2 grams of ceftriaxone intravenously once daily and 750 milligrams of acyclovir intravenously three times a day for 14 days which resulted in reduction of neurological deficit. The patient underwent logopaedic treat-

ment. He was discharged from the hospital and recommended to take doxycycline 100 milligrams orally twice daily for the next 14 days. Neurological, gastroenterological, and logopaedic follow-up examinations were foreseen.

RESULTS

LD is diagnosed based on three criteria: positive epidemiological history, presence of signs and symptoms associated with BB infection, and typical finding with a predictive value of the diagnosis such as EM or by laboratory confirmation (2). Considering facial and abducens palsy, MRI is used to exclude differential diagnosis such as compressing lesion, brainstem infarct, perineural tumour spread or focal lesion, inflammatory aetiologies, multiple sclerosis, and sarcoidosis (6). CSF typically shows lymphocytic pleocytosis with plasma cells, activated lymphocytes, and a significant increase in total protein or albumin ratio with lactate levels slightly above normal values (1), and in this case CSF was normal. Laboratory diagnosis is based on the demonstration of an antibody that reacts with BB and the established approach is so-called 2-tiered testing: ELISA followed by WB if the ELISA is either positive or borderline (2). In our case, positive BB antibodies in serum and CSF were definitive findings that supported a working diagnosis of Lyme disease neuroborreliosis.

Blood test results have also shown polyclonal hypergammaglobulinemia. In a review published in 2021, polyclonal hypergammaglobulinemia was related to 114 aetiologies classified in 15 nosology groups, of which infectious diseases were among the most frequent causes (18%) and followed by non-malignant haematological conditions (16%), autoimmune diseases (15%), and hematologic malignancies (14%) (7). Despite a detailed list of the most common infectious diseases with polyclonal hypergammaglobulinemia, searching available literature, we did not find a report that specifically linked BB to this laboratory finding.

Literature was searched for similar cases that would include negative anamnestic data of EM and multiple CNPs. One American case report published in June 2021 was found. The patient described in a report was a young female from a Lyme endemic region who presented with bilateral sixth CNP and a dilated right pupil, a partial third CNP and facial nerve palsy. MRI of her brain showed enhancement of CN III, V, VI, VII, VIII, IX, and X symmetrically. MRI of the spine also showed diffuse enhancement of the cauda equina nerve roots and enhancement of nerve roots throughout the cervical spine. Her CSF analysis revealed a lymphocytic pleocytosis and detection of Lyme IgM and IgG bands by WB (8).

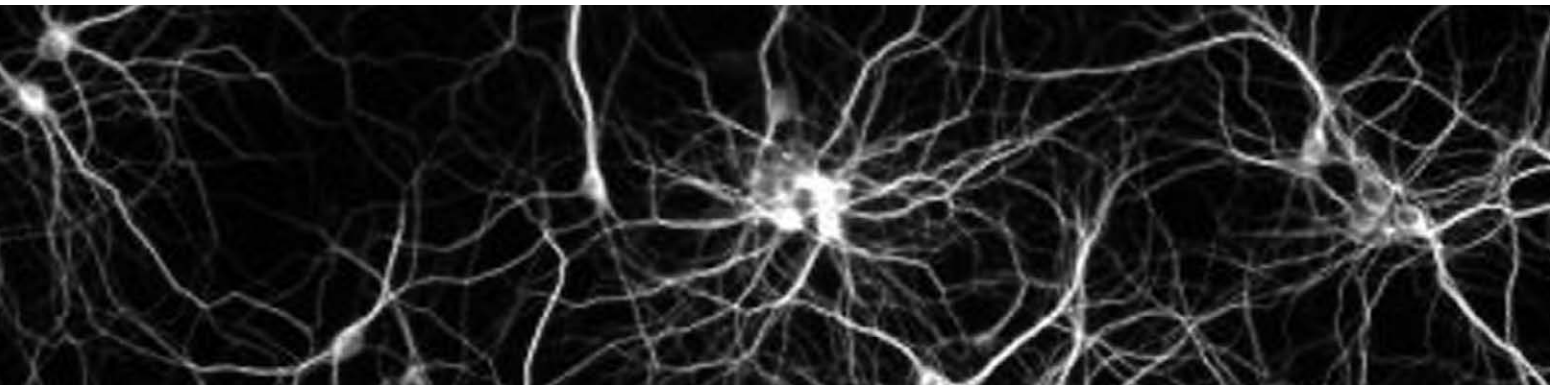
CONCLUSION

To conclude, bilateral facial palsy and unilateral abducens palsy with normal CSF and MRI findings, as described in our case presentation, have not yet been described in the literature. Besides the rare presentation, CNP with normal CSF and MRI findings should be differentially diagnostic considered as neuroborreliosis. Relations and underlying pathophysiology between polyclonal hypergammaglobulinemia and BB infection should be further investigated. Early diagnosis and treatment of the acute onset of LD is important for preventing dissemination of the infection and further complications.

REFERENCES

1. Rauer S, Kastenbauer S, Hofmann H, *et al*. Guidelines for diagnosis and treatment in neurology – Lyme neuroborreliosis. GMS Ger Med Sci. 2020; 18: Doc03
2. Halperin JJ. Neuroborreliosis. Neurol Clin. 2018 Nov;36(4):821-830.
3. Cardenas-de la Garza JA, De la Cruz-Valadez E, Ocampo-Candiani, J, *et al*. Clinical spectrum of Lyme disease. Eur J Clin Microbiol Infect Dis 38, 201–208 (2019).
4. Ross Russell AL, Dryden MS, Pinto AA, Lovett JK. Lyme disease: diagnosis and management. Pract Neurol. 2018 Dec;18(6):455-464.
5. Summer G, Rupprecht TA. Rev Neurol (Paris). 2019 Sep-Oct;175(7-8):417-419.
6. Lindland ES, Solheim AM, Andreassen S, et al. Imaging in Lyme neuroborreliosis. Insights Imaging. 2018 Oct;9(5):833-844.
7. Beuvon C, Martin M, Baillou C, Roblot P, Puyade M. Etiologies of Polyclonal Hypergammaglobulinemia: A scoping review. Eur J Intern Med. 2021 Aug; 90:119-121.
8. Sriram A, Lessen S, Hsu K, Zhang C. Lyme Neuroborreliosis Presenting as Multiple Cranial Neuropathies. Neuroophthalmology. 2021 Jul 23;46 (2):131-135.

Address for correspondence: Paula Božić; E-mail: paullabozic@yahoo.com



Combined surgical and Gamma Knife treatment of extremely rare hypopharyngeal squamous cell carcinoma brain metastasis in the eloquent region

Manuela Frančić[1], Niko Njirić[1,2,6], Biljana Đapić Ivančić[3], Antonija Jakovčević[4], Vesna Bišof[5], Romana Perković[3], Jakob Nemir[1,2,6]

ABSTRACT – *Objectives*: To present a successful treatment of brain metastasis of hypopharyngeal squamous cell carcinoma by combined surgical and Gamma Knife treatment. *Case description*: We report a 65-year-old male presenting in the emergency room with moderate left hemiparesis and a mild frontal headache. In the past year, he was diagnosed with hypopharyngeal cancer stage IVA (T4a, N0, M0) and has been treated surgically and with adjuvant radiation therapy. He was in complete remission. Contrast-enhanced magnetic resonance imaging showed a right-sided cystic lesion 5.4 x 5.2 cm in size in the basal ganglia, with peripheral contrast enhancement. Diffusion restriction and high relative cerebral blood volume (rCBV) values were recorded. An extensive zone of perifocal edema was affecting the white matter of the frontal lobe on the right. A midline shift of 10 mm to the left was noted and the right lateral ventricle was compressed. *Results*: Surgery was performed. The pathohistological finding indicated the metastasis of squamous cell carcinoma. Tissue was made up of solid clusters of atypical, moderately to well-differentiated squamous epithelial cells focally forming horny beads. The residual part of the metastasis was treated by Gamma Knife Radiosurgery, two weeks after surgery. Three-month follow-up confirmed the absence of neurological deficits and no progression of the intracranial process. *Conclusion*: Patients with hypopharyngeal squamous cell carcinoma and brain metastasis can attain complete intracranial remission after surgical treatment followed by Gamma Knife Radiosurgery.

Keywords: brain metastasis, Gamma Knife Radiosurgery, pharyngeal cancer

[1] School of Medicine, University of Zagreb, Zagreb, Croatia
[2] Department of Neurosurgery, University Hospital Centre Zagreb, Zagreb, Croatia
[3] Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia
[4] Department of Pathology and Cytology, University Hospital Centre Zagreb, Zagreb, Croatia
[5] Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia
[6] EURACAN

INTRODUCTION

Brain metastases are the most common intracranial malignancies in adults. Even though pharyngeal cancer has significant metastatic potential spreading not only to regional (lateral neck and retrolatero-pharyngeal) lymph nodes but also to distant sites, cases of hypopharyngeal cancer brain metastases are extremely rare. We report a patient with a hypopharyngeal tumor that was treated by resection followed by radiosurgery with a good result of disease control.

CASE REPORT

The patient is a 65-year-old male presenting in the emergency room with moderate left-sided hemiparesis. He reported having a mild frontal headache for a few days and noticed weakness in the left side of his body for the past two weeks. No other neurological abnormalities were noted. A year ago he was diagnosed with hypopharyngeal cancer stage IVA (T4a, N0, M0). Laryngectomy and partial hypopharyngectomy with modified radical neck dissection type I were performed and the pharynx was reconstructed using the pectoralis major myocutaneous flap. After tracheostomy, a tracheoesophageal voice prosthesis was placed. Following a surgical procedure, the patient underwent 32 cycles of adjuvant radiation therapy with a total dose of 64 Gy. In the past year, regular check-ups by the oncologist confirmed the remission of the cancer with no signs of local recurrence or dissemination of the disease.

Neuroimaging was performed (shown in Fig. 1.a and 1.b). Contrast-enhanced magnetic resonance imaging (MRI) showed a right-sided cystic lesion 5.4 x 5.2 cm in size in the basal ganglia, with peripheral contrast enhancement. Diffusion restriction and high relative cerebral blood volume (rCBV) values were recorded on the perfusion scans. An extensive zone of perifocal edema was affecting the white matter of the frontal lobe on the right. Midline shift of 10 mm to the left was noted and the right lateral ventricle was compressed with no signs of hypertensive hydrocephalus. Neuroimaging scans indicated the presence of brain metastasis or high-grade glial tumor, primarily a glioblastoma.

The patient was treated surgically. A frontotemporoparietal right-sided osteoplastic craniotomy was performed. The cystic tumor process was verified, the contents were evacuated and sent for microbiological analysis. The rest of the tumor mass was reduced to the greatest extent possible. During the resection of the posteromedial infiltrative part, the neuromonitoring showed a decline in motor evoked potential (MEP) and somatosensory evoked potential (SSEP), so we left a small tumor remnant for Gamma Knife treatment because we wanted to preserve maximum quality of life of the patient after surgery. Tissue samples were taken for pathohistological analysis. Postoperatively, he was hemodynamically stable, afebrile, without signs of infectious disease. Postoperative MEP and SSEP were completely normal. His motor deficits were recovering. Vancomycin-resistant *Enterococcus faecium* was identified in the cyst content and patient was given linezolid. Pathohistological analysis showed tumor tissue made up of solid clusters of atypical, moderately to well-differentiated squamous epithelial cells focally forming horny beads, and was partly necrotic (shown in Fig. 2.). With finding corresponding to the metastasis of squamous cell carcinoma, the definite diagnosis was established. The residual part of the metastasis as

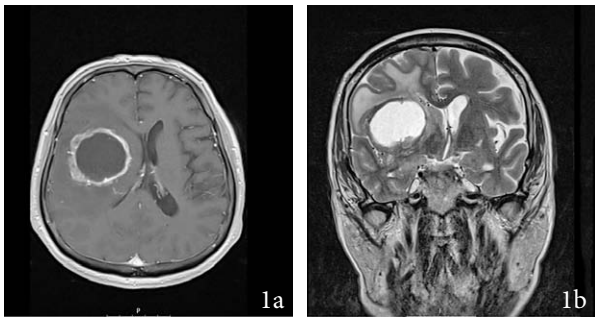


Fig. 1.a *Preoperative axial contrast-enhanced T1-weighted MR image showing a right-sided cystic lesion in the basal ganglia, with peripheral contrast enhancement.*
Fig. 1.b *Preoperative coronal T2-weighted MR image showing a right-sided cystic lesion in the basal ganglia with large perifocal edema in the frontal white matter.*

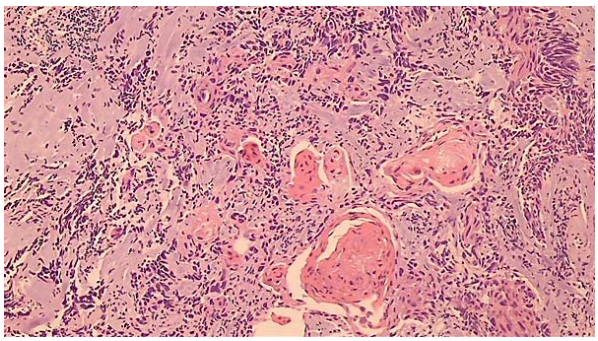


Fig. 2. *Squamous cell carcinoma made up of solid clusters of atypical, moderately to well-differentiated squamous epithelial cells focally forming horny beads (HE 100x).*

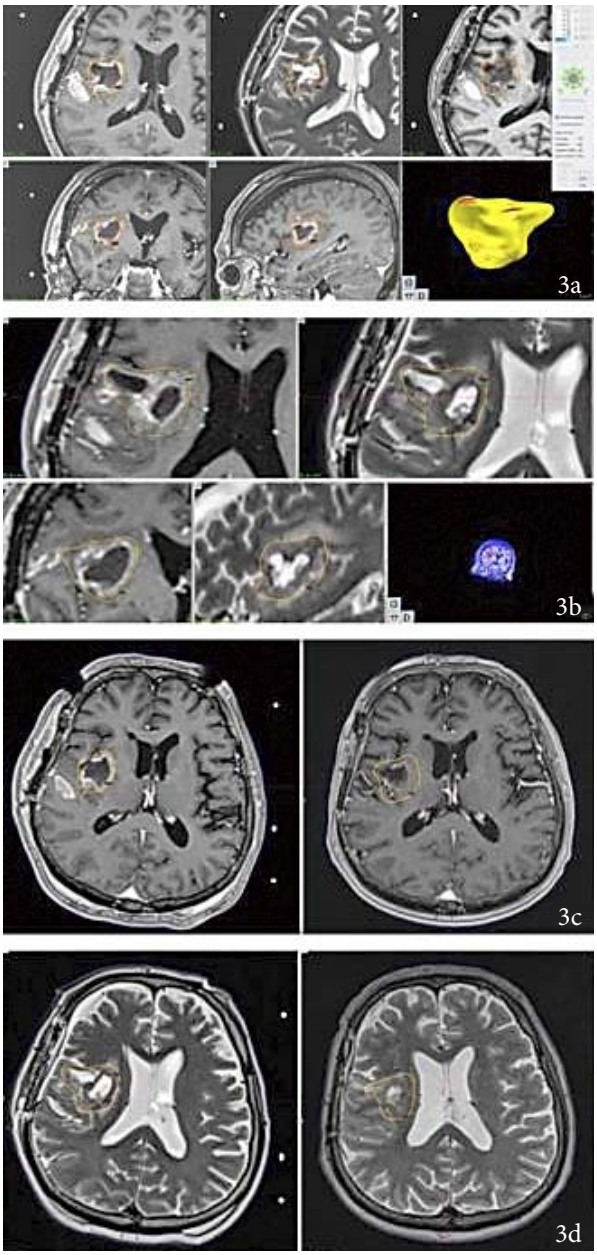


Figure 3.a-3.d. *Gamma Knife Radiosurgery planning snapshots: a prescription dose of 19 Gy to prescription isodose 59% was administered to the residual tumor, two weeks after surgery.*

well as the resection cavity were verified by MRI and treated by Gamma Knife Radiosurgery. Considering the volume of the postoperative tumor site of 13,193 cm^3, we decided to give a dose of 19 Gy to prescription isodose 59% to the residual tumor, two weeks after surgery (shown in Fig. 3.). There were no complications during nor after the procedure. Significant regression of the treated tumor site was seen on later brain MRI. Three and seven-month follow-ups confirmed the absence of neurological deficits and no progression of the intracranial process (shown in Fig. 4.).

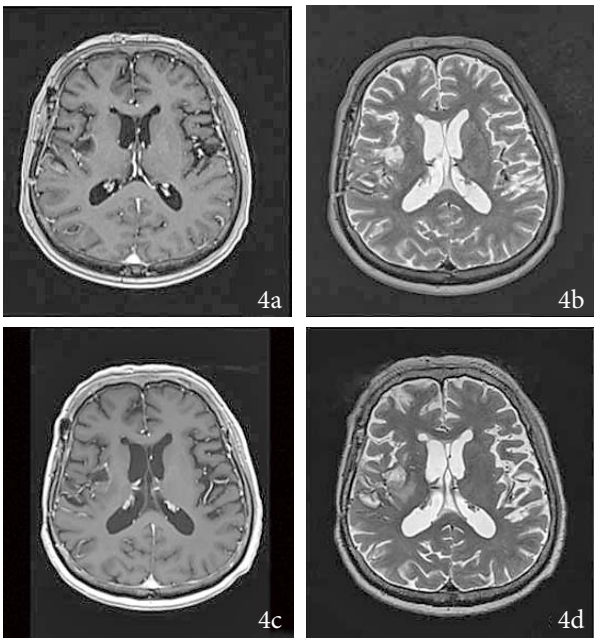


Fig. 4. *Three months (4.a) and seven months (4.c) after surgery and Gamma Knife Radiosurgery - axial contrast-enhanced T1-weighted MR image showing a significant reduction of the tumor volume. Three months (4.b) and seven months (4.d) after surgery and Gamma Knife Radiosurgery - coronal T2-weighted MR image showing no signs of perifocal edema surrounding the operative cavity.*

DISCUSSION

The most common neurologic manifestation of systemic cancer is brain metastases. Based on patient's clinical presentation and past history data, differential diagnosis can be narrowed. However, the radiologic differential diagnosis of metastasis is difficult since imaging findings are similar to those of high-grade gliomas (HGG). Because of a blood-brain barrier disruption, both are seen on perfusion MRI as ring-enhancing lesions with surrounding edema. Some authors suggest using peritumoral rCBV for distinguishing metastases from glioblastoma, but the accuracy of this method remains controversial. Magnetic resonance spectroscopy (MRS) has great potential, yet its clinical utility is limited. Diagnostic accuracy may be improved by using combination of advanced imaging protocols, including diffusion, perfusion, and MRS of peritumoral regions. Apart from that, many physiologic and imaging biomarkers and their abilities to define cellularity, angiogenesis, perfusion, pH, hypoxia, may have a prognostic value and further advance diagnosis and treatment. For now, definite diagnosis is made based on pathohistological analysis, but MRI remains the modality of choice for monitoring the response to treatment

(1). A minimally invasive procedure of stereotactic biopsy with evacuation of the cystic content and obtaining a pathohistological sample can be offered to patients not suitable for the procedure under general anesthesia. However, considering that after the evacuation of the cyst the planned target point for sampling changes, stereotactic biopsy carries a high risk of obtaining an inconclusive pathohistological finding. Since the tumor was operable, the biopsy was not performed in our case. With the aim of reduction of disabling neurological symptoms, tumor mass effect, as well as preventing the dissemination of tumor cells with a stereotactic needle, the mainstay of treatment for our patient was resection followed by Gamma Knife Radiosurgery. Whole-brain radiotherapy has a great impact on cognitive function and results in poorer overall quality of life, while Gamma Knife Radiosurgery enables the application of high focal doses of radiation to a volume with low toxicity to adjacent brain structures (2) and has proven to be a great method of treating residual tumor mass.

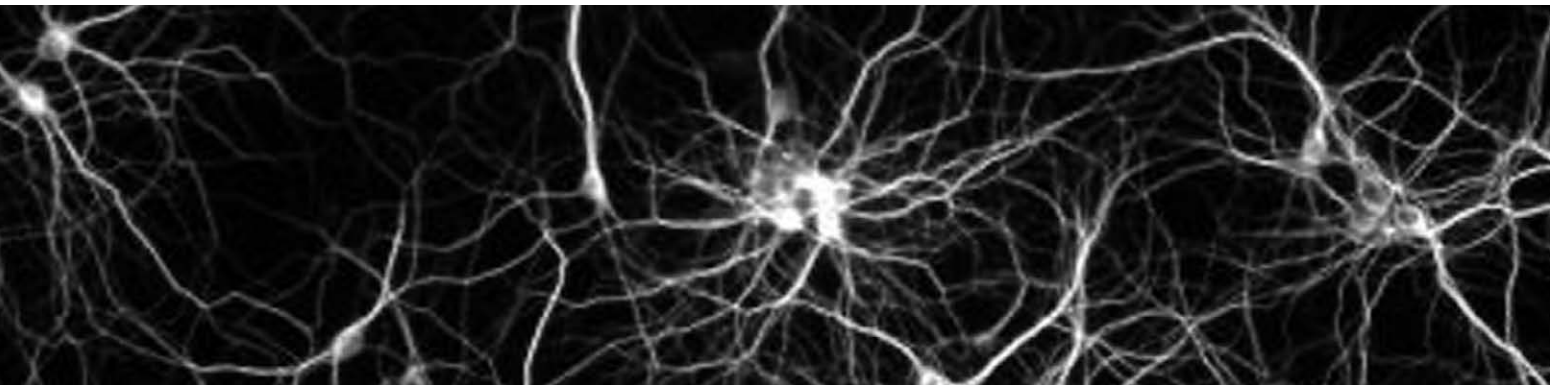
CONCLUSION

Patients with hypopharyngeal squamous cell carcinoma and brain metastasis can attain complete intracranial remission after surgical treatment followed by Gamma Knife Radiosurgery.

REFERENCES

1. Pope WB. Brain metastases: neuroimaging. Handb Clin Neurol. 2018;149:89–112.
2. Wolf A, Kondziolka D. Brain metastases: radiosurgery. Handb Clin Neurol. 2018;149:129-135.

Address for correspondence: Manuela Frančić; E-mail: manuela.francic2@gmail.com



Anesthesiological approach to intrathecal baclofen overdose

Monika Kocman Panić[1], Jadranka Premužić[1], Ivan Koprek[2], Nenad Kudelić[2], Renata Krobot[1], Anita Lukić[1], Slobodan Mihaljević[3]

ABSTRACT – *Objectives:* We report two cases of intrathecal baclofen overdose, clinical course, and management. Our aim is to educate healthcare workers about possible choices for the management of intrathecal baclofen overdose. *Case description:* A 61-year-old patient with spastic tetraparesis and baclofen pump therapy was admitted to the intensive care unit due to neurological deterioration and respiratory depression. He required periodic increases in the dosage of intrathecal baclofen and antipsychotic drugs for baclofen psychosis. On admission, he was hemodynamically unstable, and laboratory results indicated inflammation and hyperglycemia. Second patient, a 29-year-old, with also spastic tetraparesis and baclofen pump therapy, was admitted to the intensive care unit after pump manipulation with neurological deterioration and bradycardia. Both patients fully recovered after symptomatic treatment and reduction of intrathecal baclofen delivery to a minimum. *Conclusion:* Being one of the few centers in Croatia in which implanting and managing patients with baclofen pump is done, we need to be prepared to solve the adverse effects of baclofen such as overdose, always having in mind there is no antidote for baclofen, and that there are no guidelines for the management.

Keywords: intrathecal baclofen, overdose, spine trauma

INTRODUCTION

Baclofen is a gamma-aminobutyric acid (GABA) derivative acting as a presynaptic and postsynaptic agonist of $GABA_B$ receptors (1,2,3,4). Since it relieves the spasticity, it is used to treat muscle spasms of cerebral and spinal origin caused by various neurological disorders, such as after brain injury (including posttraumatic brain injury and

[1] Department of Anesthesiology, Reanimatology and Intensive Care, General Hospital Varaždin, Varaždin Croatia

[2] Department of Neurosurgery, General Hospital Varaždin, Varaždin, Croatia

[3] University Department of Anesthesiology, Reanimatology and Intensive Medicine and Pain Therapy, University Hospital Centre Zagreb and School of Medicine University of Zagreb, Zagreb, Croatia

stroke), cerebral palsy, upper motor neuron syndrome, or by spinal cord disorders, such as spinal cord injury (4,5). Oral baclofen is mainly water-soluble and does not easily cross the blood-brain barrier so higher doses are needed of the same effect as intrathecal baclofen (3,5). The concept supporting intrathecal therapy is the delivery of baclofen directly to the site of action, the spinal cord, via a programmable pump implanted in the abdominal wall, which enables the delivery of smaller doses avoiding the systemic side effects. It is suggested that the tip of the intrathecal catheter should be placed at the T1–T2 level for spastic quadriplegia, the T6–T10 level for spastic diplegia, and in the midcervical region for dystonia (6). Intrathecal baclofen has been demonstrated to improve significantly daily activities, but it is not without complications (7). The most serious complication is overdose, usually caused by a malfunctioning pump, keeping in mind there is no antidote for baclofen and that there are no national guidelines for the management (3,6).

Being one of the few institutions in Croatia implanting baclofen pumps for spams caused by spinal trauma, we present here the clinical course, encountered problems, and management of two cases of intrathecal baclofen overdose.

CASE REPORT

PATIENT 1

In the 61-year-old male with spastic tetraparesis after cervical spine trauma and following surgery at the level C6-C7, the baclofen pump (*Syncromed II, Medtronic, Minneapolis, Minnesota, USA*) was implanted in August 2017, following a successful baclofen trial. Required dosage increase of intrathecal baclofen periodically since 2017 and since February 2021 in therapy with antidepressant because of baclofen psychosis.

He was admitted to the hospital in May 2022 with a progression of spasticity and psychotic elements (would not eat or drink). The psychiatrist adjusted the psychiatric therapy (olanzapine/haloperidol, diazepam, lorazepam). Following the evening psychiatric therapy, the next morning, the patient was admitted into the intensive care unit (ICU) due to deterioration of clinical state: Glasgow coma scale score 3, miosis, but breathing spontaneously. The patient was intubated and mechanically ventilated, and fluid therapy (crystalloids) with diuretics (furosemide) was initiated, while the baclofen pump infusion was decreased to a minimal flow (96mcg/day). Since the patient was hemodynamically unstable (blood pressure 80/40 mmHg), continuous vasopressor support was initiated (noradrenaline 6-15mcg/kg/h). Computed tomography (CT) of the brain showed no signs of ischemia or hemorrhage, but chest radiography showed signs of pneumonia.

Laboratory results indicated inflammation (CRP 196 mg/L normal range <5.0mg/L, neutrophils 7.27×109/L- normal rage 2.06-6.49x109/L, lymphocytes 0.73×109/L – normal range 1.19-3.35x109), and hyperglycemia of 19.7 mmol/L (4.4-6.4mmol/L).

After 19 hours of mechanical ventilation and supportive therapy, the patient fully recovered, with no neurological symptoms, and baclofen therapy was continued.

PATIENT 2

In the 29-year-old male patient with incomplete spastic tetraplegia after cervical spine trauma at level C4 and surgery, the baclofen pump (*Syncromed II, Medtronic, Minneapolis, Minnesota, USA*) was implanted in March 2019, following a successful baclofen trial. He was admitted to the hospital due to the suspected baclofen pump malfunction, but the malfunction was excluded with the CT.

On the day of admission to the ICU, the patient showed bradypnea (7 breaths/minute), bradycardia (40 beats/minute), sopor, and was only reactive to the pain. Therefore, the baclofen pump infusion was decreased to minimum flow (96 μg/day) and the flow modality was changed. The laboratory results were within normal ranges, except for the lymphocyte count (1.13×109/L normal range 1.19-3.35x109). Symptomatic therapy was administered (atropine boluses of 1 milligram), with fluid therapy (crystalloids) and diuretics (furosemide).

The patient was fully recovered after several hours. He was discharged from the ICU with no new neurological symptoms, and the baclofen therapy was continued.

DISCUSSION

Intrathecal baclofen, administered via baclofen pump, is delivered directly to the site of its action in the spinal cord, bypassing the blood-brain barrier entirely. Acting as presynaptic and postsynaptic agonists of $GABA_B$ receptors (1,2,3,4), intrathecal baclofen downregulates receptor sensitivity, so

there is a potential risk for tolerance over time. Despite the fact that the number of baclofen receptors is decreased, it is the baclofen that can cause suppression of neuronal activity (2).

Manifestations of a baclofen overdose include respiratory depression, diffuse hyporeflexia, diffuse hypotonia, coma, hypothermia, bradycardia/tachycardia, delirium, seizures, and cardiac arrhythmias (1,2,4,8). The deterioration can be rapid and may even require cardiopulmonary resuscitation (9).

The most common cause of overdose is malfunction of the pump in the majority of cases (90%). Mechanical flow problems are common, so it is important to confirm pump and catheter localization. Overdose can also occur as a result of iatrogenic mistake, by incorrect re-filling of the pump or by to high infusion rate (3,6).

Overdose could easily occur as a result of increased baclofen infusion rate, in order to mitigate aggravated spasticity caused by noxious stimuli. Namely, the noxious stimuli (i.e., urinary tract infections, constipation) increase the afferent input (incoming nerve message to the CNS) on the stretch reflex (10).

In our patients, we confirmed the correct position and functioning of the baclofen pump. Therefore, the possible cause of baclofen toxicity/overdose in the first patient could be the concomitant psychiatric therapy that acted as respiratory depressants. Also, we could stipulate that inflammation caused the alternation of pharmacodynamics and pharmacokinetics of baclofen, although it has not been investigated previously. In the second patient, we suspected that the overdose occurred due to the pump manipulation during re-filling.

Regardless of the cause of the baclofen overdose, the problem is that there is no antidote for baclofen. It has been shown that atropine and neostigmine administration, or the lumbar punction and cerebrospinal fluid drainage, along with supportive care (fluids, diuretic, mechanical ventilation) have been successful in sporadic cases (2,3,4).

The additional problem could pose the potential development of serious withdrawal symptoms after a baclofen overdose in patients who have been receiving baclofen chronically. Therefore, it is important to reinstate the baclofen administration under strict monitoring, once the overdose symptoms are gone (1).

CONCLUSION

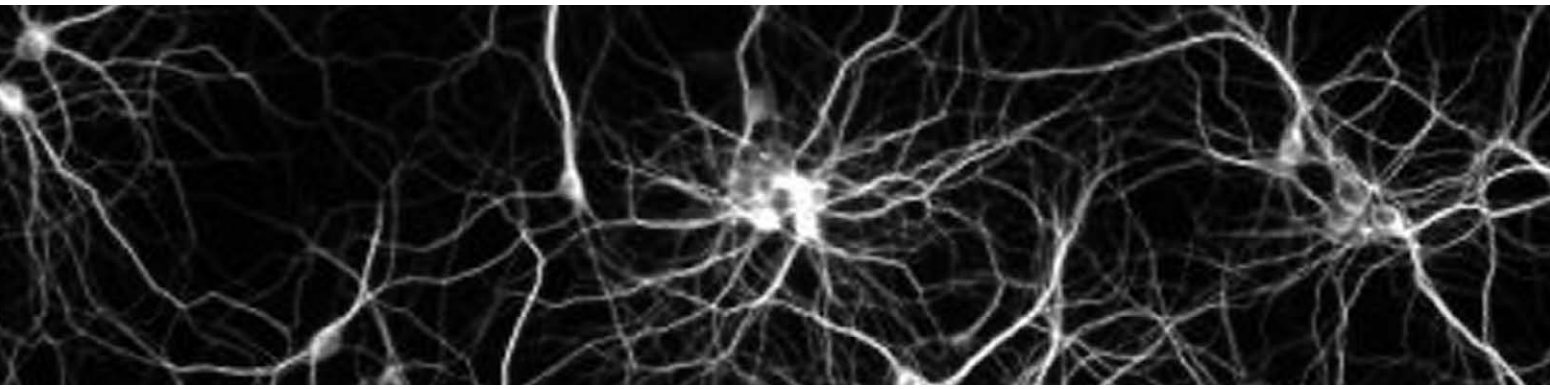
Patient with intrathecal baclofen pump are at possible risk of serious adverse events, such as acute baclofen overdose. There is no antidote for baclofen, so the current therapeutic efforts for baclofen overdose are directed towards minimizing intrathecal delivery of baclofen and lowering the availability of baclofen for binding to receptors, with the concomitant employment of symptomatic therapy.

In the setting of no official guidelines for baclofen overdose, case reports such as this are a valuable source of therapy for the clinicians and a possible foundation for the guidelines development.

REFERENCES

1. Miller JJ. Baclofen overdose mimicking anoxic encephalopathy: a case report and review of the literature, Ther Adv Drug Sal, 2017, 8(5), 165-167
2. Darbari FP, Melvin JJ, Piatt, JH, Adirim TA, Kothare SV. Intrathecal Baclofen Overdose Followed by Withdrawal: Clinical and EEG Features, Pediatr Neurol 2005;33:373-377.
3. Tunali Y, Hanimoglu,H, Tanriverdi T, Hanci L, Hanci M. Intrathecal Baclofen Toxicity and Deep Coma in Minutes, J Spinal Cord Med. 2006;29,237–239
4. Kramer K, Weber M, Koulousakis A, Lier A, Krep H. Intrathekale Baclofentherapie Überdosierung beim Wechselder Medikamentenpump, Anaesthesist 2009, 58, 891–896
5. Ertzgaard P, Campo C, Calabrese A. Efficacy and safety of oral baclofen in the management of spasticity: A radionale for intrathecal baclofen, J Rehabil Med 2017; 49: 193–203
6. Gburek-Augustat J, Krause M, Bernhard M, *et al.* Unusual mechanical failures of intrathecal baclofen pump systems: symptoms, signs, and trouble shooting, Childs Nerv Syst, 2021;37(8): 2597- 2604
7. Watve SV, Sivan M, Raza W A, Jamil FF. Management of acute overdose or withdrawal state in intrathecal baclofen therapy, Spinal Cord, 2012; 50:107–111
8. Paskhin DL, Dekopov AV, Tomskiy AA, Isagulyan ED, Salova EM. Complications of Intrathecal Baclofen Therapy, Zh Vopr Neirokhir N.N. BURDENKO, 2017;81(1):63-69
9. Gidon Winter G, Beni- Adani L., Ben-Pazi H. Intrathecal Baclofen Therapy—Practical Approach: Clinical Benefits and Complication Management, J Child Neurol, 2018;33(11):734-74.
10. Francisco GE, Saulino M, Yablon SA, Turner M. Intrathecal Baclofen Therapy: An Update, PM&R, 1(9), 2009;852-858.

Address for correspondence: Monika Kocman Panić; E-mail: monika.kocman88@gmail.com



Marchiafava–Bignami disease: a rare but not forgotten complication of chronic alcoholism

Žana Kralj[1], Josipa Fiamengo[2], Gordana Glavina[3], Krešimir Dolić[3,5], Gordan Džamonja[4,5]

ABSTRACT – *Objectives:* To report of rare case of Marchiafava-Bignami disease (MBD), which is, to the best of our knowledge, the first to be described in Croatia. *Case description*: A 50-year-old woman, who consumed 200–500 mL hard liquor daily during a 2-year period, was admitted to hospital due to dysfunctionality, general weakness, and gradual cognitive impairment. *Results:* After her state of consciousness deteriorated to the level of sopor, urgent brain magnetic resonance imaging (MRI) was performed showing extensive lesions in the corpus callosum and subcortical white matter, bilaterally. As clinical presentation, accompanied by MRI finding, was strongly suggestive of MBD, we immediately started therapy with high-dose vitamin B complex and methylprednisolone over five days. After two weeks, a control MRI showed significant regression of the callosal and other white matter lesions. During and after treatment, the patient gradually started regaining consciousness and a natural cycle of wakefulness and sleep, but lack of verbal skill and dysphagia persisted. Further treatment focused on nutritional support, alcohol abstinence, physical and speech therapy. After a 2-year period of rehabilitation, her cognitive performance had improved markedly (MoCA was 24/30), with mild residual deficits in several cognitive domains. On examination slight gaze palsy to the left persisted, accompanied by weaker left plantar response, and mild spastic dysarthria. She moved into her own house with her sister. *Conclusion*: Although the disease is potentially fatal, a timely diagnosis based on clinical and radiological evidence and prompt treatment can result in a quite favorable final prognosis, as shown in our case.

Keywords: chronic alcoholism, corpus callosum, demyelinating disorders, Marchiafava-Bignami disease, thiamine

[1] Department of Psychiatry, University Hospital of Split, Split, Croatia
[2] Psychiatric Hospital Ugljan, Ugljan, Croatia
[3] Department of Radiology, University Hospital of Split, Split, Croatia
[4] Department of Neurology, University Hospital of Split, Split, Croatia
[5] University of Split, School of Medicine, Split, Croatia

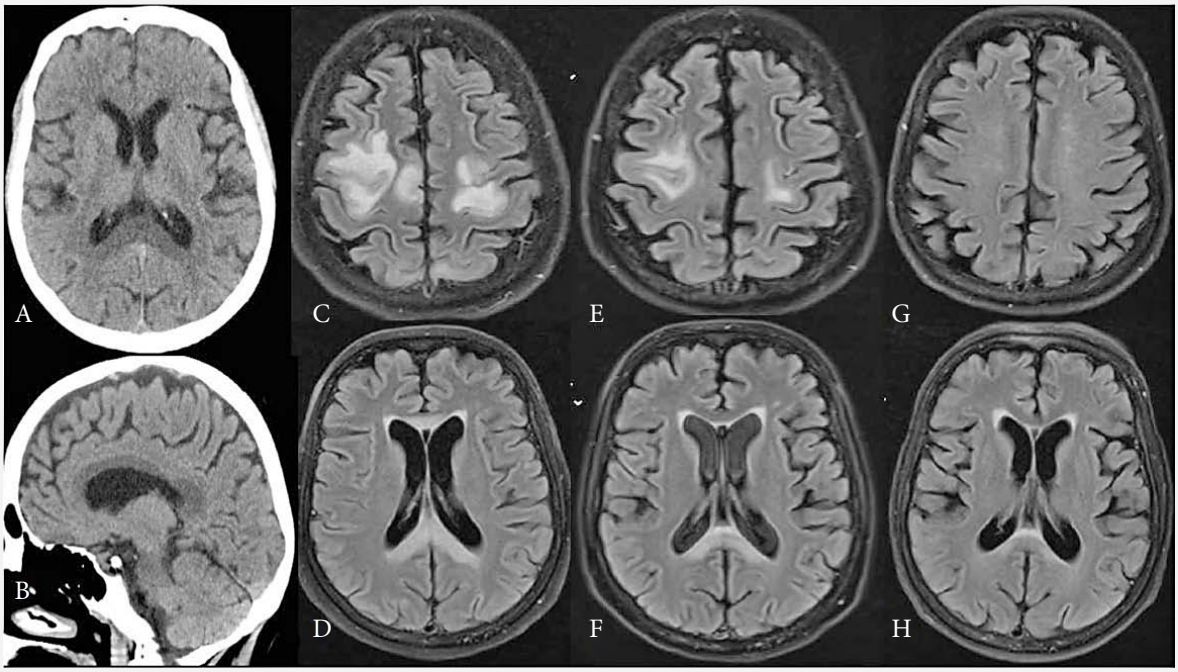


Fig. 1. *A axial, and B sagittal brain CT images showing edema of the splenium of the CC; C-H axial FLAIR images: C-D acute onset of the disease: prominent frontal bilateral white matter and CC lesions; E-F first follow-up brain MRI: moderate regression of brain lesions; G-H second follow-up brain MRI: almost complete regression of the brain lesions*

INTRODUCTION

Marchiafava–Bignami disease (MBD) is a rare demyelinating disorder associated mostly with severe and chronic alcohol abuse and/or malnutrition leading to a deficiency in vitamin B complex (1). Its incidence is higher in middle-aged men with a history of chronic alcoholism (2). The clinical presentation of MBD is nonspecific and can vary from mild motor and cognitive disturbances to coma and death; thus, early-stage MBD is difficult to diagnose or differentiate from other diseases (1,3). In addition to the clinical picture, modern brain imaging, especially magnetic resonance imaging (MRI), is crucial for prompt diagnosis, because timely treatment can remarkably increase the survival rate (1,4).

CASE DESCRIPTION

A 50-year-old woman admitted to the Department of Psychiatry for dysfunctionality and lack of motivation to abstain from chronic alcohol consumption had, during a 2-year period, consumed 200–500 mL hard liquor daily. One month before hospitalization, she started complaining of general weakness and occasional leg muscle cramps, which were accompanied by gradual cognitive impairment. As her state of consciousness deteriorated from somnolence to sopor, she was transferred to the Department of Neurology.

On admission, the patient's Glasgow coma score was 9. Dysphagia and paratonia were evident, but no signs of meningeal irritation, focal motor deficits, or pathologic reflexes were present. We performed a computed tomography (CT) scan of the brain which showed edema of the splenium of the corpus callosum (CC) bilaterally (Fig. 1, A-B). As her clinical condition was further deteriorating, we ordered a brain MRI for more detailed information. The MRI showed extensive bilateral lesions in the frontal subcortical and deep white matter region at the level of vertex and in the genu and splenium of CC, but also some lesions in the parietal and occipital regions. The lesions were hyperintense on FLAIR (Fig. 1, C-D) and T2WI images, with some signs of restricted diffusion and minor enhancement inside frontal lesions. The cerebrospinal fluid assay revealed moderate proteinorahia and just 1 leukocyte, with no signs of intrathecal immunologic activity. An electroencephalogram was remarkably slowed, without epileptiform discharges. *Escherichia coli* was isolated from urine. No deficit of folic acid or vitamin B12 was detect-

ed. Thyroid function tests were normal and antithyroid antibodies were negative.

Because the clinical presentation and MRI findings were consistent with a diagnosis of MBD, we immediately started therapy with high-dose vitamin B complex (B1, folate, B12) and intravenous methylprednisolone (1250 mg total) over five days. The urinary infection was treated with co-amoxiclav. After two weeks, total protein in the cerebrospinal fluid had decreased to almost normal, a test for JCV was negative, and follow-up MRI showed significant regression of the callosal and frontal white matter lesions (Fig. 1, E-F). During and after treatment, the patient gradually started regaining consciousness and a natural cycle of wakefulness and sleep; however, lack of verbal skill and dysphagia persisted. Further treatment focused on nutritional support and rehabilitation from alcoholism.

The patient was discharged to a long-term care facility that provided physical and intensive speech rehabilitation. Follow-up MRI of the brain 12 weeks after the initial imaging revealed almost complete regression of the brain lesions (Fig. 1, G-H). After a 2-year period of rehabilitation and alcohol abstinence, the patient's electroencephalogram was normal. Her cognitive performance had improved markedly (Montreal Cognitive Assessment: 24/30), with mild residual deficits in the areas of attention, visual–spatial skills, left–right orientation, and praxia. During a neurologic exam, her walk was unimpaired, but slight gaze palsy to the left persisted, accompanied by a brisker left patellar reflex, weaker left plantar response, and mild spastic dysarthria. She left the care facility and moved into a house with her sister.

DISCUSSION

The pathologic changes typical in MBD were first described by two Italian pathologists, Ettore Marchiafava and Amico Bignami, in 1903. The syndrome includes symmetrical demyelination and necrosis of the central part of the CC, with relative sparing of the dorsal and ventral layers (1). Later, it became evident that the pathology could additionally affect the subcortical white matter, basal ganglia, and even the brain cortex (5,6). Those changes are most frequently encountered in chronic alcoholism and other malnourishment but might also be observed in paraneoplastic syndromes or osmotic myelinolysis (2). The precise mechanism of the damage in MBD, including the selective vulnerability of the CC, is still not entirely elucidated, but synergism between ethanol-induced neurotoxic effects and hypovitaminosis B, particularly B1, is suggested to be the most plausible (7).

Although MBD occurs in both sexes, most cases are seen in men (2). The clinical spectrum of the disease is broad and lacks specificity (1). Its features can vary from mild motor and cognitive disturbances to severe motor deficits, disordered coordination, impaired consciousness, signs of interhemispheric disconnection, seizures, and ultimately death (3). Based solely on clinical manifestations, the first MBD classification (8) distinguished acute, subacute, and chronic forms. Subsequently, in 2004, with the advent of modern brain imaging, Heinrich *et al.* proposed a clinicoradiological classification of type A - with distinguishing clinical features of stupor or coma, accompanied by pyramidal signs, and imaging revealing involvement of almost the entire CC like it was in our case, or type B - normal or mildly perturbed mentation, with signs of focal callosal lesions on imaging (9). In the early 2000s, MBD was still considered a rather rare and almost invariably fatal disorder (10). But given that alcoholism is a common problem, MBD was more likely to have been underdiagnosed in the preimaging era. Data suggest that the overall outcome of MBD has improved notably in recent decades (4), partly because of increased awareness and because of the broader availability of MRI.

On MRI, a characteristic "sandwich sign" represents the involvement of the central layers of the CC body, with relative sparing of the dorsal and ventral extremes on sagittal views. In our case, the lesions were in the genu and splenium of CC, which is more common in MBD mimics but also can be seen in one-third of the MBD subjects (1). On the other hand, no lesion enhancement has been described in the MBD mimics: it is more common in real MBD like it was in our case. The CC might appear edematous in the acute phase and atrophic in the chronic phase (11). The clinical and radiologic presentations contribute equally to a quick diagnosis. The mainstay of therapy is prompt parenteral thiamine replacement (1). When MBD is suspected, disorders from the differential such as infarction of the recurrent artery of Heubner, neoplastic diseases (astrocytoma or lymphoma, for instance), demyelinating diseases such as multiple sclerosis, progressive multifocal leukoencephalopathy, or acute disseminated encephalomyelitis should first be excluded. Among the demyelinating diseases to be excluded, multiple sclerosis is the most common but occurs in a different clinical setting (11).

In our case, the diagnosis was made based on the history of chronic alcoholism and radiologic features. Diagnostic workup was limited to a certain extent as some tests like measurements of blood thiamine level or autoimmune encephalitis antibodies have not been available in our center. Although the patient initially had a severe subacute type A case of MBD, prompt treatment and long-term rehabilitation led to a favorable clinical outcome.

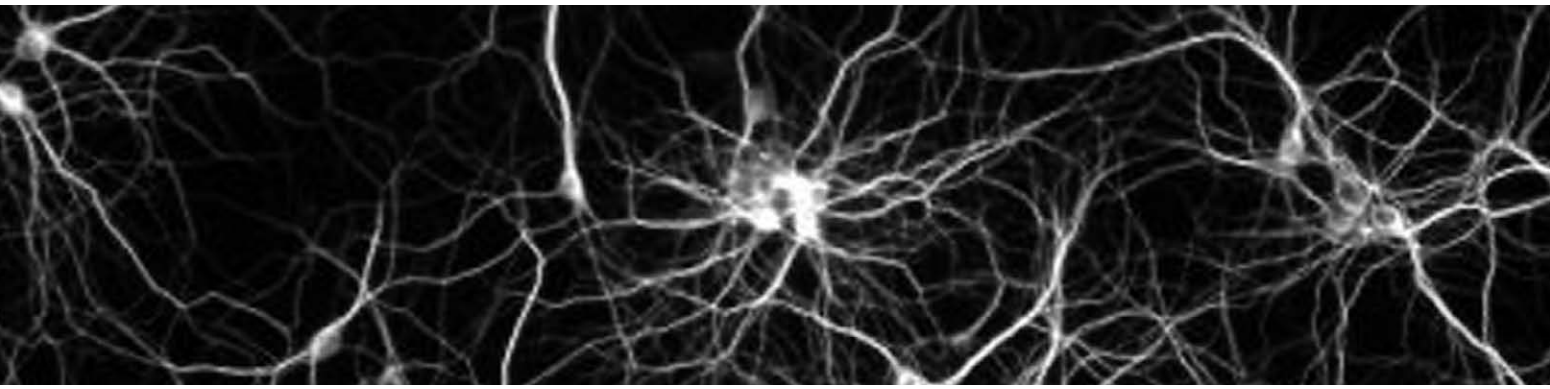
CONCLUSION

To the best of our knowledge, this case of MBD is the first described in Croatia. Given that the manifestations of MBD are nonspecific, early clinical suspicion coupled with timely brain imaging were crucial for effective treatment and avoiding a potentially fatal outcome in this case.

REFERENCES

1. Hillbom M, Saloheimo P, Fujioka S, Wszolek ZK, Juvela S, Leone MA. Diagnosis and management of Marchiafava–Bignami disease: a review of CT/MRI confirmed cases. J Neurol Neurosurg Psychiatry. 2014;85:168–173. doi:10.1136/jnnp-2013-305979
2. Wenz H, Eisele P, Artemis D, Förster A, Brockmann MA. Acute Marchiafava–Bignami disease with extensive diffusion restriction and early recovery: case report and review of the literature. J Neuroimaging. 2014;24:421–424. doi:10.1111/j.1552-6569.2012. 00755.x
3. Muccio CF, De Lipsis L, Belmonte R, Cerase A. Reversible MR findings in Marchiafava–Bignami disease. Case Rep Neurol Med. 2019;2019: 1951030 doi:10.1155/2019/1951030
4. Kinsley S, Giovane RA, Daly S, Shulman D. Rare case of Marchiafava–Bignami disease due to thiamine deficiency and malnutrition. BMJ Case Rep. 2020;13:e238187. doi:10.1136/bcr-2020-238187
5. Kawarabuki K, Sakakibara T, Hirai M, Yoshioka Y, Yamamoto Y, Yamaki T. Marchiafava–Bignami disease: magnetic resonance imaging findings in corpus callosum and subcortical white matter. Eur J Radiol. 2003;48:175–177. doi:10.1016/S0720-048X (02)00349-2
6. Parmanand HT. Marchiafava–Bignami disease in chronic alcoholic patient. Radiol Case Rep. 2016; 11:234–237. doi:10.1016/j.radcr.2016.05.015
7. Fernandes LMP, Bezerra FR, Monteiro MC, *et al.* Thiamine deficiency, oxidative metabolic pathways and ethanol-induced neurotoxicity: how poor nutrition contributes to the alcoholic syndrome, as Marchiafava–Bignami disease. Eur J Clin Nutr. 2017;71:580–586. doi:10.1038/ejcn.2016.267
8. Brion S. Marchiafava–Bignami disease. In Vinken PJ & Bruyn GW (eds): Handbook of Clinical Neurology. 317–329. Elsevier, Amsterdam, 1977.
9. Heinrich A, Runge U, Khaw AV. Clinicoradiologic subtypes of Marchiafava–Bignami disease. J Neurol. 2004;251:1050–1059. doi:10.1007/s00415-004-0566-1
10. Helenius J, Tatlisumak T, Soinne L, Valanne L, Kaste M. Marchiafava–Bignami disease: two cases with favorable outcome. Eur J Neurol. 2001;8:269–272. doi:10.1046/j.1468-1331.2001.00212.x
11. Kumar KS, Challam R, Naveen J, Singh WJ. Marchiafava–Bignami disease: a case report. J Clin Diagn Res. 2014;8:RD01–RD02. doi:10.7860/JCDR/2014/8377.4668

Address for correspondence: Gordan Džamonja; E-mail: dzamonja.gordan@st.t-com.hr



CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

Denis Čerimagić[1], Ervina Bilić[2]

Keywords: neuroinflammatory diseases, lymphocytes, pons, magnetic resonance imaging, steroids

A 71-year-old man was referred for a neurological examination due to instability. Dysphonia, dysphagia, and ataxia were present in neurological examination, while punctate and curved gadolinium enhancement "peppering" lesions of the pons and the cerebellar peduncles were present in the MRI of the brain (Figs. 1–3). The MRI of the cervical spine was normal. The CSF analysis revealed only mild lymphocytic pleocytosis (cell count 30/3). The oligoclonal bands were negative in CSF and serum (type 1). The results of ACE, immunological tests, tumor markers, and serological tests for neurotropic pathogens, as well as testing for HIV, lues, and tuberculosis, were normal. The patient was treated with high-dose IV methylprednisolone (1 g/day) for five consecutive days, followed by a taper with oral steroids for six months, after which complete clinical and neuroradiological remission was achieved (Figs. 4 and 5). Based on the results of these findings, the diagnosis of CLIPPERS was established. CLIPPERS is a rare neuroinflammato-

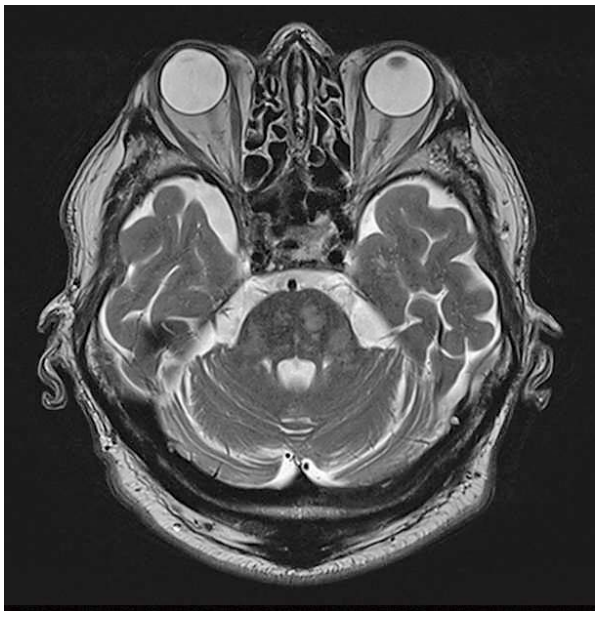


Fig. 1. *Axial T2WI MRI shows multiple punctate and patchy regions in the pons and cerebellar peduncles.*

[1] Polyclinic Glavić and University of Dubrovnik, Dubrovnik, Croatia

[2] Department of Neurology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

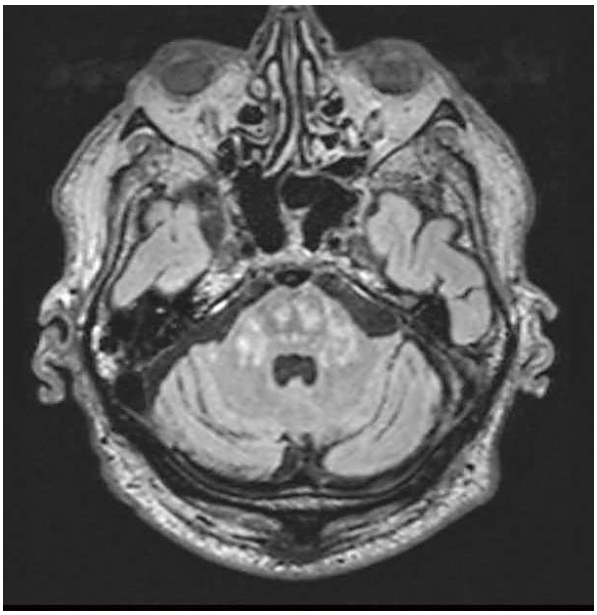


Fig. 2. *Axial FLAIR MRI shows multiple punctate and patchy regions in the pons and cerebellar peduncles.*

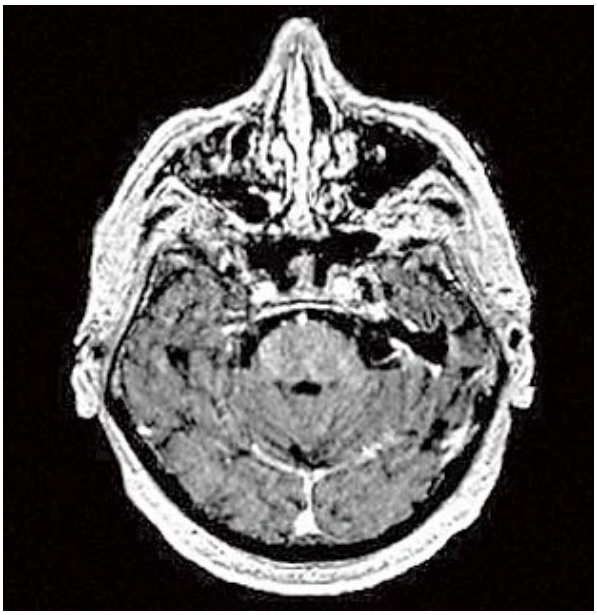


Fig. 3. *Axial contrast-enhanced T1WI MRI shows punctate foci of contrast enhancement in the pons.*

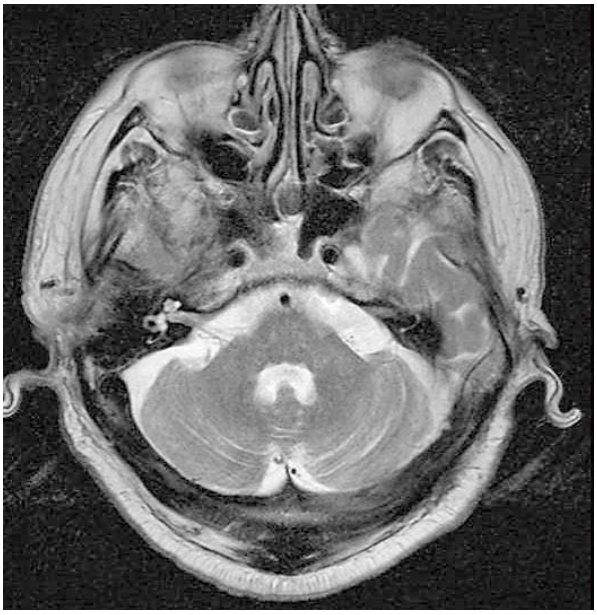


Fig. 4. *Control axial T2WI MRI shows normal findings.*

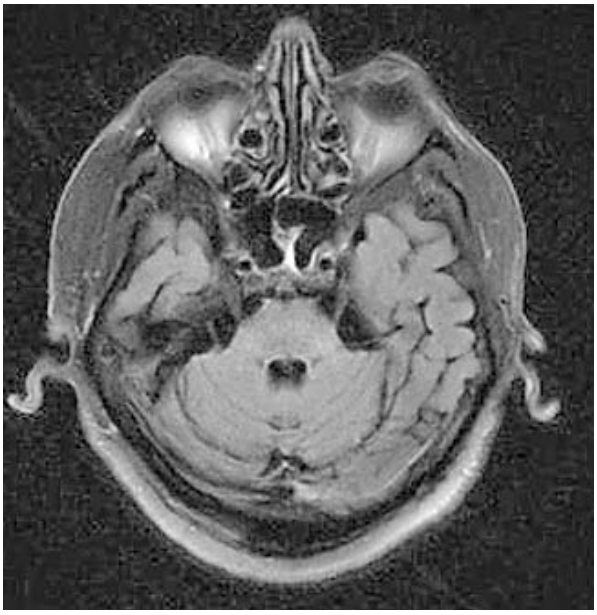


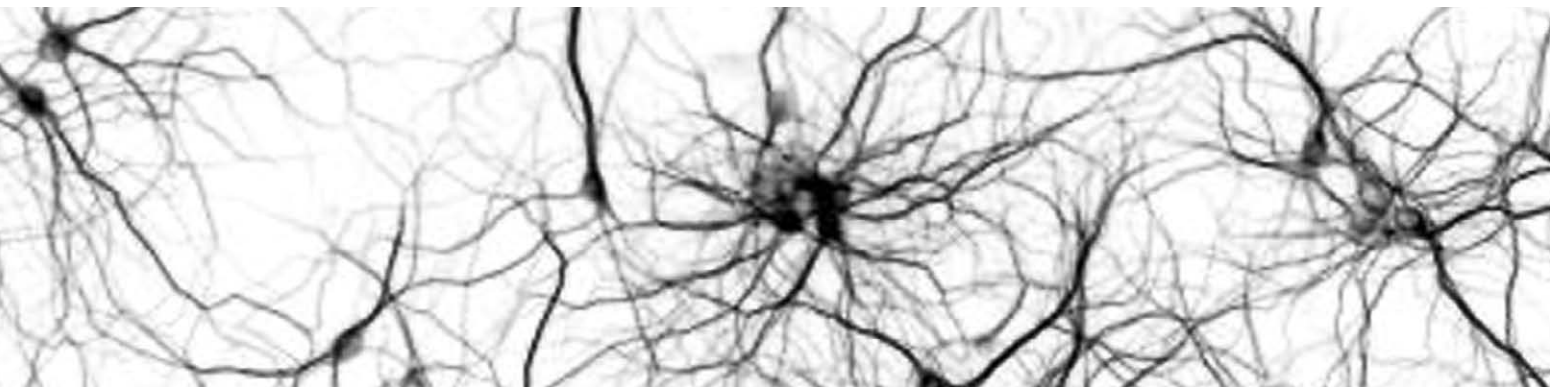
Fig. 5. *Control axial FLAIR MRI shows normal findings.*

ry disorder characterized by brainstem-predominant encephalomyelitis that typically presents with cerebellar (ataxia) and bulbar involvement (dysarthria, dysphagia), typical MRI findings, and an excellent therapeutic response to steroid administration (1, 2). It is to be expected that the broader availability of highly sensitive neuroradiological diagnostics will naturally contribute to the efficacy and accuracy of finding this disease.

Address for correspondence: Denis Čerimagić; E-mail: deniscerimagic@yahoo.com

REFERENCES

1. Axelerad AD, Stroe AZ, Mihai C, *et al.* CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids: A challenge in neurological practice, clinical landmarks (Review). Exp Ther Med 2021;22:1191.
2. Shrestha NM, Acharya N, Desar R. Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS Syndrome): A Case Report and Literature Review. Case Rep Neurol Med 2023;2023:5811243.



Authors index
for volume 68/2023

Authors index – vol. 68/2023.

Begović M. 69
Benić I. 77
Bilić E. 69, 102
Bišof V. 91
Bogdan Veljković K. 77
Borovečki F. 87
Božić P. 87
Čerimagić D. 102
Dolić K. 98
Džamonja G. 98
Đapić Ivančić B. 91
Fiamengo J. 98
Frančić M. 91
Glavina G. 98
Jakovčević A. 91
Klepac N. 87
Kocman Panić M. 95
Koprek I. 95
Kralj Ž. 98
Krobot R. 95
Kudelić N. 95
Lukić A. 95
Mihaljević S. 95
Nemir J. 91
Njirić N. 91
Perković R. 87, 91
Petelin Gadže Ž. 69
Poljaković-Skurić Z. 77
Premužić J. 95

Instructions to authors

NEUROLOGIA CROATICA, the official journal of the Croatian Neurological Society and Croatian Neurosurgical Society, is published semi-annual by University of Zagreb, School of Medicine and University Hospital Centre Zagreb, Department of Neurology.

Neurologia Croatica brings articles covering clinical neurology, basic neuroscience, and other related fields.

Neurologia Croatica publishes the following types of articles:

1. Original contributions: Maximum length is 3000 words, excluding tables, figure legends, and references. Total word count should be provided with each manuscript including abstract, all text, tables, figure legends, and references.
2. Neurological reviews: Reviews are usually solicited by the editors, however, spontaneous submissions are also welcome. All articles and data sources reviewed should include information about the specific type of study or analysis, population, intervention, exposure, and test or outcomes. All articles or data sources should be selected systematically for inclusion in the review and critically evaluated, and the selection process should be described in the paper. Maximum length: the same as for original contributions.
3. Case reports: Case reports need to have important and novel learning points and report on unusual syndromes or diseases; a simple narrative or challenging patient(s) is insufficient. Maximum length is 1500 words, excluding tables, figure legends, and references.
4. Images in neurology: This feature is intended to provide a visual image of an interesting and unique neurological observation. Images of patients along with images of diagnostic proceedures performed are welcome. Maximum length is 200 words for case description, 50 words for each figure, maximum of 2 references.
5. Letters to the editor: Letters discussing a recent Neurologia Croatica article are welcome. Letters should be received within 3 months of the article publication. Short comments on topical issues of public interest are also possible. Maximum length is 500 words including all text, tables, figure legends, and references.

In addition, announcements of professional and scientific meetings will be published.

Authors are responsible for the authenticity of data and for methodologic acceptability.

Submission of a manuscript implies that it is submitted exclusively to this journal and its contents have not been published previously except in abstract form.

A statement confirming the copyright transfer to Neurologia Croatica signed by the first author is necessary for publication.

Author Guarantee Statement. You can download the Author Guarantee Statement form on the journal's homepage Author Guarantee Statement. This form should be filled in and signed by the first author of the manuscript, scanned and e-mailed together with the manuscript. All manuscripts without signed Author Guarantee Statement will be returned to the author.

All articles are subject to review; referees are selected by the Editorial Board. Author(s) may suggest three potential referees (include names, full address, phone & fax numbers and e-mail) in the covering letter.

MANUSCRIPT PREPARATION

The form and contents of the manuscript should be carefully checked.

All manuscripts should be written in English, with additional abstract and key words in Croatian. Manuscripts with illustrations attached and Author Guarantee Statement, prepared according to the instructions below, should be sent by mail as hard copy in triplicate, two of these without the names of authors and institutions, and by e-mail to the Editor-in-Chief's address/e-address. Authors should keep copies of the original manuscript and other related material, since the materials received will not be returned to the authors.

The editor retains the right to shorten the material accepted for publication if necessary.

The complete manuscript, including text, figures, tables and references, should be typed on one side of the paper only, double-spaced, with 3-cm left margin and right margin not justified. Each paragraph should be indented by five spaces.

Author should mark in the margin where figures and tables are to be inserted.

Each section should start on a new page (i.e. title page, abstract, figures, tables, legends and references).

The title page should comprise:

1. title of the paper;
2. full name of each author followed by the highest academic degree and institutional affiliation (all institutional names should be written in English);
3. name, accurate address, phone & fax numbers and e-mail of the author responsible for correspondence, galley-proofs and reprints;
4. short title, not longer than 30 characters including spaces;
5. acknowledgment of the source(s) of support.

Abstract should be no longer than 250 words. Original contributions should have structured abstracts with the following headings: objectives, methods, results and

conclusions. Abstract for Neurological reviews should not be structured. Case reports should have structured abstract with the following headings: objectives, case description, results, conclusion. Images in neurology and letters to the editor do not require an abstract. It should only present the main results and avoid general formulations and well-known facts.

Three to ten key words should be supplied in alphabetical order immediately following the abstract.

Please search for the key words at the web page http://www.ncbi.nlm.nih.gov/pubmed/, link MeSH Database.

Text should be divided, when appropriate, into sections: Introducion, Material and Methods, Results, Discussion, and Conclusion.

Scientific papers, including the list of references, should not exceed 12 pages (32 lines with 60 characters each per page), and brief communications 3 pages.

Tables should be typed on separate sheets, not to be submitted as photographs. Illustrations should be provided unmounted, in the form and condition suitable for reproduction. Freehand drawings, raw laboratory material, e.g., strip charts, roentgenograms, etc., should be photographed in B/W. Photographs should not be larger than 20x25 cm. If the attachements are in color (tables, photographs, etc.), the author should pay for the expenses of printing that page in agreement with Denona Printing House.

For every photograph of a recognizable patient written permission is required.

The author(s) should be aware that the size of illustrative material may be reduced if needed.

Tables and figures should be numbered in Arabic numerals in the order they are mentioned in the text. Legends for each of them should be typed separately, each legend on a separate sheet. The number of figures should not exceed 6.

List of references should include only those works that are cited in the text and that have been accepted for publication or already published.

The list should be arranged according to the order of appearance in the text and then numbered.

Several works of the same first author should be listed chronologically by the year of publication. Index Medicus abbreviations of journal names should be used.

REFERENCES

Journals

All authors to be listed in case there are six or less:

Mubrin Z, Kos M. Assessment of dementia. Flow chart approach to clinical diagnosis. Neurol Croat 1992;41: 141-156.

If the article is written by seven or more authors, only names of the first three authors should be listed, followed by et al.:

Baršić B, Lisić M, Himbele J, et al. Pneumococcal meningitis in the elderly. Neurol Croat 1992;41:131-140.

Books

Critchley M. The ventricle of memory. New York: Raven Press, 1990.

Chapter in a book

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

In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975:1-9.

Citations of works in text should be indicated by numbers in brackets.

Reprints of the published article should be ordered before publication.

Thirty reprints are free of charge, and additional reprints will be provided at publishing prices.

MAILING INFORMATION

All manuscripts, with illustrations and Author Guarantee Statement enclosed should be E-MAILED as an attachment ONLY to the Editor-in-Chief to the following e-mail address: neurologiacroatica@kbc-zagreb.hr

Prof. Mario Habek, MD, PhD, Editor-in-Chief, Neurologia Croatica, University of Zagreb, School of Medicine, University Hospital Centre Zagreb, Department of Neurology, Kišpatićeva 12, HR-10000 Zagreb, Croatia; e-mail: mhabek@mef.hr

Duodopa®

LEVODOPA/CARBIDOPA INTESTINAL GEL

SAMO ZA ZDRAVSTVENE RADNIKE
HR-DUOD-230024, kolovoz 2023.

SAMO ZA ZDRAVSTVENE RADNIKE

AJOVY®▼: Jedini registrirani *anti-CGRP* lijek koji omogućuje fleksibilno kvartalno i mjesečno doziranje[1]

AJOVY® je indiciran za profilaksu migrene u odraslih koji imaju migrenu najmanje četiri dana na mjesec.[1]

DOSTUPAN KAO NAPUNJENA BRIZGALICA

- **Terapijski izbor koji nudi dobru podnošljivost[1,2]**
- **Manje dana s migrenom u odnosu na placebo već od 1. tjedna[1]**
- **Ispitano uz istodobno uzimanje oralnih preventivnih lijekova i bez njih[1]**
- **Dokazana djelotvornost, čak i kod bolesnika čiju je migrenu teško liječiti*[2]**

Pomozite pacijentima reći DA za više trenutaka

▼ Ovaj je lijek pod dodatnim praćenjem. Time se omogućuje brzo otkrivanje novih sigurnosnih informacija. Od zdravstvenih radnika se traži da prijave svaku sumnju na nuspojavu za ovaj lijek. Upute za prijavljivanje dostupne su na **www.halmed.hr**

*Bolesnici čiju je migrenu teško liječiti bili su oni s epizodnom i kroničnom migrenom kod kojih je dokumentiran neuspjeh 2 do 4 skupine lijekova za prevenciju migrene[2]

Napomena: Upućujemo zdravstvene radnike na posljednji cjelokupni sažetak opisa svojstava lijeka te uputu o lijeku AJOVY®, koji je dostupan na internetskoj stranici Agencije za lijekove i medicinske proizvode (http://www.halmed.hr). **Način izdavanja:** na recept, u ljekarni.
Datum sastavljanja: ožujak 2023, AJO-HR-00102

PLIVA HRVATSKA d.o.o., Prilaz baruna Filipovića 25, 10000 Zagreb, Hrvatska
Tel.: +385 1 37 20 000, Faks: +385 1 37 20 111 **www.pliva.hr, www.plivamed.net**

Reference: 1. Sažetak opisa svojstava lijeka za AJOVY® odobren 7.6.2022. **2.** Ferrari MD et al. Lancet 2019; 394(10203): 1030-1040.

AJOVY®
(fremanezumab)
otopina za injekciju 225 mg/1,5 mL