The association of paroxysmal hemicrania with trigeminal neuralgia (TN) has been described and called paroxysmal hemicrania-tic syndrome (PH-tic).

We report the case of a patient diagnosed as having chronic PH-tic (CPH-tic) syndrome as a clinically isolated syndrome of the central nervous system (CNS) (CIS).

A forty year old woman was admitted to our hospital suffering from right facial pain for the last 2 years. The attacks were paroxysmal, neuralgiform, consisting of throb-like sensations, which developed spontaneously or were triggered by different stimuli in right facial (maxilar and mandibular) areas. Parallel with those, she felt a throbbing orbital and frontal pain with homolateral autonomic symptoms such as conjunctival injection, lacrimation, and the feeling that the ear on the same side was full. This pain lasted most often between 15 and 20 minutes.

Beyond hemifacial hypoesthesia in the region of right maxilar and mandibular nerve, the other neurological finding was normal. Magnetic resonance imaging (MRI) study showed a T2-weighted multiple hyperintense paraventricular lesion and hyperintense lesion in the right trigeminal main sensory nucleus and root inlet, all of them being hypointense on T1-weighted image. All of these lesions were hypointense in gadolinium-enhanced T1-weighted images. Neurophysiological studies of trigeminal nerve (somatosensory evoked potentials and blink reflex) correlated with MRI described lesions. The patient’s pain bouts were improved immediately after treatment with indomethacin, and were completely relieved with lamotrigine for a longer period. According to the actual McDonald’s criteria, clinical state was defined as CIS which was clinically presented by CPH-tic syndrome.

Even though it is a clinical rarity and its etiology is usually idiopathic, CPH-tic syndrome can also be symptomatic. When dealing with symptomatic cases, like the one described here, when causal therapy is not possible due to the nature of the primary pathological process, a therapeutic approach, although symptomatic, can be fully effective in controlling this painful syndrome. The case report could be a contribution to the pathophysiological and clinical understanding of the association of CPH and TN.

Key words: Paroxysmal hemicrania, trigeminal neuralgia, clinically isolated syndrome

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Trigeminal autonomic cephalalgias (TACs) are a group of primary headaches characterized by unilateral headache and the presence of cranial autonomic phenomena on the side of the headache. This group includes cluster headache, paroxysmal hemicrania (PH), short-lasting unilateral attacks of neuralgiform headaches, hemicrania continua, and a group of headaches marked as possible trigeminal autonomic headaches (1).

TACs are usually idiopathic conditions, while in
5–10% they occur as a consequence of pathological processes of viscerocranium and neurocranium, inflammatory, vascular, neoplastic, or traumatic etiology (1,2). The diagnosis of TACs is clinical and it is based on the knowledge of diagnostic criteria for each TAC defined in the International Classification of Headache Disorders (ICHD-III beta). The biggest challenge in diagnosing TACs is their differentiation in relation to other short-lasting headache syndromes, including trigeminal neuralgia (TN), especially its atypical forms (3).

On the other hand, patients who had a TAC and TN, marked as TAC-tic syndrome, were described. TAC-tic syndromes represent a clinical rarity whose etiology is usually idiopathic, but in a smaller number of cases it can be an unusual clinical manifestation of other pathological conditions (4,5).

Recognizing a TAC-tic syndrome is important, because for each of these conditions there are recommendations for achieving complete immediate and long-term therapeutic effects, but it is also significant for conducting therapy for primary diseases in case of symptomatic TAC-tic syndrome (3). Studying clinical and paraclinical TAC-tic syndromes could also be a contribution to the understanding of pathophysiological mechanisms of correlation of these 2 different clinical phenotypes of headaches.

Taking into account the aforementioned facts, the authors present the case of a patient with newly diagnosed symptomatic chronic paroxysmal hemicrania (CPH)-tic syndrome which was clinically presented as a clinically isolated syndrome of the central nervous system (CNS) (CIS).

**Case Report**

The patient, 40 years of age, was sent to the hospital for examination and treatment, due to the pain in the right half of the face, general weakness, and weight loss. The pain in the right half of the face, in the area of the upper and lower jaw and nose started 2 years before. She described the pain as sharp, stabbing, like a needle puncture, lasting a few seconds, never more than a minute ("like I was electrocuted"), of a very high intensity (visual analog scale [VAS] 9/10), without spreading to the surrounding area of the face. The pain was not accompanied by nausea or retching. During the attack of the strongest pain, the muscles contracted on the side of the pain, sometimes there was redness of the eye and lacrimation. The pain attacks occurred in the morning, first spontaneously, and then more often, provoked by common actions (washing the face, touching, chewing, …), dozens of times a day.

General hematological and biochemical blood analyses were performed in her health center, as well as examination by a dentist and an ear, nose, and throat (ENT) specialist, and the results were normal. A nonspecific analgesic and polyvitamin therapy was started. After a few days of analgesic use and short-term, incomplete pain release ("as if the pain will start, but there is no strong pain"), problems of the same characteristics reappeared; they were of a very high intensity, occurred dozens of times a day, sometimes the pain attacks flew into one another. The patient noticed a more frequent "somewhat different," very strong pain (VAS 10/10) "spreading" to the area of eye and forehead, during which her eye was red and tearful, and she had a feeling that her ear was full. Some attacks lasted longer than before, from 15 to 20 minutes.

In her health center she was diagnosed having TN. A therapy with pregabalin at a daily dose of 150 mg was started. After a month without therapeutic efficacy, the therapy was replaced by gabapentin at a daily dose of 600 mg. After a month, due to no pain release, a therapy with carbamazepine at a daily dose of 200 mg was introduced. The daily dose of the drug was supposed to be gradually increased up to a dose of 800 mg. After the introduction of carbamazepine, the pain in the face (lower and upper jaw) was less intense. However, the patient experienced a constant day-to-day dull pain, the intensity was described as mild to moderate, sometimes becoming very sharp in the forehead area and the depth of the eye, followed by eye redness and lacrimation. She did not increase the daily dose of carbamazepine over 400 mg, because she noticed that by increasing the dose she became very unstable, had vertigo, and felt general weakness.

A year after the problems had started (6 months after introducing therapy with carbamazepine), due to the inability of increasing the dose of carbamazepine and due to daily pain, an additional therapy was introduced – amitriptyline with gradual dose increase up to 75 mg a day. After the use of amitriptyline the patient felt better for a while (without constant pain between the attacks of intense pain in the forehead area), but the attacks of pain similar to a needle puncture in the area of nose and lower jaw occurred frequently again, while pain in the area of the right eye and right half of the forehead lasting 15 to 20 minutes occurred more often. It was accompanied by a feeling of fullness of the ear at the same side, redness of the eye, and lacrimation.
Since chewing provoked puncture pain, the patient gradually reduced food intake; she lost 18 kg and became mentally tense (“I am waiting for the next attack”), slept badly, and became socially isolated. She complained of extreme instability and general weakness.

Before these problems occurred she had been perfectly healthy. She denied the presence of diseases in her family history which could be significant for the actual condition.

When she was admitted at the Clinic of Neurology of the Clinical Centre Nis, her mental status was characterized by bradypsychia, anxiety with reactive characteristics, with an increase on the scale of hypochondriasis, without the elements of psychopathological manifestation (performed neuropsychological assessment); besides arterial hypotension with reactive tachycardia, there was no other medical finding related to the physical status; the neurological status was characterized by hypoesthesia for all modalities of sensation in the areas of innervations of the maxillar and mandibular nerve on the right side. Weakness of fixation on the upper and lower limbs on the left side was noticed while testing gross motor skills, although without lateralization of the finding, and without other specific findings.

Hematological and biochemical diagnostics were performed (serum level of thyroid hormones, immunological blood analysis for the purposes of quantifying parameters of immunological systemic disorders) – all the findings were in the frame of reference. The results of cytological biochemical assessment of liquor were regular. Rendgen of paranasal sinuses, examinations by an ENT, maxillofacial surgeon, ophthalmologist, and psychiatrist were without pathological findings.

Immediately after admission to hospital, the use of co-analgesic therapy was terminated (amitriptyline, carbamazepine). There was a reduction in vertigos and cardiac tachyarrhythmia, with implementation of daily parenteral hydro-mineralization and detoxification therapy (with the solution of magnesium sulfate).

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Neurophysiological Studies

Trigeminal somatosensory evoked potentials (TSEPs) were recorded with Nihon Kohden Neuropack M1 device by electrical stimulation of both infraorbital and mental branches at the site of upper and lower lips using a surface stimulating electrode. Registration AgAgCl disc electrodes were put at the C5 and C6 point of the 10 – 20 coordinate system and a reference electrode was put at the Fz position. Stimulation current strength was about 3 times the sensory threshold with 0.2 ms pulse duration at a 1 Hz repetition rate. A Lo-cut filter at 20 Hz and Hi-cut filter at 20 kHz, sensitivity of 10 microV/div and 50 ms of analysis time, were used to average 50 responses.

Blink reflex was performed by stimulating both supraorbital nerves over the supraorbital foramina, using a single pulse current of 0.2 ms duration and 3 times the motor threshold strength. Active recording electrodes were sited over the mid lower half of orbicularis oculi muscles and reference electrodes were placed 20 mm laterally. The additional electrodes were put over both sides of the orbicular oris muscle with reference electrodes placed 20 mm laterally in order to record responses eventually caused by ephaptic transmission. The passband was 20 to 3000 Hz, sensitivity 200 microV, and analysis time 100 ms.

Right side infraorbital TSEP showed (Fig. 2a) slightly longer N13 wave latency (normal range 9 – 15.4 ms, side diff. 2 ms), and together with right mental branch TSEP had smaller amplitude than the left side TSEPs.

Figure 2b shows normal R1 and R2 latencies of re-
responses obtained from both ipsilateral orbicularis oculi muscles, and no responses over orbicularis oris muscles (Normal values: R1 < 13 ms, diff. 1.2 ms; R2 < 41 ms, diff. 8.0 ms).

**Diagnosis and Therapy**

According to McDonald’s criteria (6), the patient was diagnosed with CIS. After excluding contraindications by a cardiologist and a gastroenterologist, an indomethacin test has been performed (using indomethacin in a daily dose of 150 mg during 3 days along with gastroprotective therapy). After the second day, the patient did not have longer-lasting pain accompanied with lacrimation and redness of the eye and the feeling of fullness at the ear on the same side. Then, the use of indomethacin was continued in a daily maintenance dose of 100 mg, with gastroprotective therapy for the next 3 weeks, with gradual termination of therapy in the last week. In accordance with the fulfillment of criteria of ICHD-III (Table 1), CPH was diagnosed.

In addition, in accordance with the fulfillment of ICHD-III criteria (Table 1), the patient was diagnosed with symptomatic TN – painful trigeminal neuropathy due to demyelinating plaque. After terminating the use of the previous co-analgesic therapy, the use of lamotrigine was introduced; the daily dose was 50 mg, with a gradual increase of the dose for 25 mg every 2 weeks. With the increase of the drug, the patient noticed that puncture pain in the lower parts of the face became rarer and started to disappear. After reaching the daily dose of 100 mg of lamotrigine, without adverse effects, and with total pain control, the patient was discharged from hospital to continue outpatient treatment.

After 3 months, at the follow-up examination, the patient was in the period of stable remission, with no pain attacks, completely mentally and physically rehabilitated.

After 6 months, there was a relapse of CPH, due to which the therapy with indomethacin, in a daily dose of 150 mg with gradual termination of therapy throughout 3 weeks, was re-introduced, along with gastroprotective therapy. After achieving absolute therapeutic efficacy, the patient did not have any more difficulties.
She continued the use of lamotrigine in a daily dose of 200 mg – without pain attacks, without worsening of the demyelinating disease.

**DISCUSSION**

On the basis of the clinical presentation of the initial difficulties, the unilateral pain in the area of innervations of the trigeminal nerve which had the characteristics of TN and which was followed by a persistent pain in the face between neuralgiform attacks, which was induced by demyelinating plaque which affected the root of the trigeminal nerve, symptomatic atypical TN was diagnosed – painful trigeminal neuropathy caused by demyelinating plaque (1). The truth is, the ICHD-III diagnostic criteria for this condition (Table 1) state that multiple sclerosis has to be diagnostically confirmed, which was not the case with our patient, since the criteria for definite MS were not fulfilled and since the criteria for CIS were fulfilled (6), the condition was understood as the initial clinical presentation of demyelinating disease...
Even though the diagnosis of these conditions is clinical, for the purposes of searching for secondary etiology and differential diagnostic consideration, additional examinations should be performed. In less than 5% of cases, TACs are caused by other pathological conditions, mostly due to hypothalamus and/or hypophysis disorders, or pathological processes in the posterior cranial fossa (vascular, neoplastic, traumatic etiology)

Table 1. Diagnostic criteria of paroxysmal hemicrania and painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque, International classification of headache disorders (ICHD-III).

<table>
<thead>
<tr>
<th>Paroxysmal hemicrania</th>
<th>Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque</th>
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<tr>
<td>A. At least 20 attacks fulfilling criteria B-E</td>
<td>A. Head and/or facial pain with the characteristics of Classical trigeminal neuralgia with or without concomitant persistent facial pain, but not necessarily unilateral</td>
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<tr>
<td>B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes</td>
<td>Classical trigeminal neuralgia</td>
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<td>C. At least one of the following symptoms or signs, ipsilateral to the pain:</td>
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<td>1. conjunctival injection and/or lacrimation</td>
<td>A. At least three attacks of unilateral facial pain fulfilling criteria B and C</td>
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<td>2. nasal congestion and/or rhinorrhea</td>
<td>B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution</td>
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<td>3. eyelid oedema</td>
<td>C. Pain has at least three of the following four characteristics:</td>
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<td>4. forehead and facial sweating</td>
<td>1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes</td>
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<tr>
<td>5. forehead and facial flushing</td>
<td>2. severe intensity</td>
</tr>
<tr>
<td>6. sensation of fullness in the ear</td>
<td>3. electric shock-like, shooting, stabbing or sharp in quality</td>
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<tr>
<td>7. miosis and/or ptosis</td>
<td>4. precipitated by innocuous stimuli to the affected side of the face</td>
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<tr>
<td>D. Attacks have a frequency above five per day for more than half of the time</td>
<td>D. No clinically evident neurological deficit</td>
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<td>E. Attacks are prevented absolutely by therapeutic doses of indomethacin</td>
<td>E. Not better accounted for by another ICHD-3 diagnosis.</td>
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<td>F. Not better accounted for by another ICHD-3 diagnosis.</td>
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Chronic paroxysmal hemicrania

Attacks of paroxysmal hemicrania occurring for more than 1 year without remission, or with remission periods lasting less than 1 month.

Diagnostic criteria:

A. Attacks fulfilling criteria for Paroxysmal hemicranias, and criterion B below
B. Occurring without a remission period, or with remissions lasting <1 month, for at least 1 year.

Even though the diagnosis of these conditions is clinical, for the purposes of searching for secondary etiology and differential diagnostic consideration, additional examinations should be performed. In less than 5% of cases, TACs are caused by other pathological conditions, mostly due to hypothalamus and/or hypophysis disorders, or pathological processes in the posterior cranial fossa (vascular, neoplastic, traumatic etiology).
Chronic Paroxysmal Hemicrania-tic Syndrome as a Clinically Isolated Syndrome of CNS

(1,15,16). It is recommended that all patients with TACs should be subjected to MRI of the endocranium. On the other hand, the appearance of TN in younger patients with the existence of clinical signs of damage of the very nerve imposes the need for obligatory neurovisualization examination with the aim of discovering symptomatic cases (1,16). However, a certain number of patients has hyperalgesia in the painful region, which could only be a consequence of patient's increased attention because of the persistent pain in the region, not of damage of the trigeminal nerve (17,18).

Before our patient was hospitalized, there had been a short and incomplete betterment of TN and persistent pain in the face due to the use of co-analggesic therapy. It is known that amitriptyline suppresses mechanisms of central sensitization and is a medicine of choice in treating chronic painful conditions, while carbamazepine is a first-line medicine of choice for treating TN (18). However, the absence of complete effect of this therapy of controlling TN could be attributed to a smaller daily dose of carbamazepine because it was impossible to increase it up to the optimal dose (17,19,20) due to potentiating of its side effects. Again, it is known that patients with symptomatic TN (painful trigeminal neuropathy attributed to demyelinating plaque) are less responsive to pharmacotherapy than the ones with classic TN (1,20).

The question that remains is: Do CPH and TN have the same pathogenetic mechanisms of origin, and is this the case of pathophysiological continuum manifested by different clinical symptoms? Co-analggesic modulation of mechanisms of chronic pain at the level endogenous analgesia system, the change of balance of adrenergic pull, Na channels blocking, membrane stabilization, extending the refractory period in afferent fibers, segmental inhibition, and reduction of excitability of the trigeminal nerve (17,19) are famous mechanisms of pain control, which were only partially efficient in our patient, and controlled only TN, not CPH. This could suggest that activation of the trigeminal nerve or trigeminal autonomous reflex is the final mutual pathogenetic mechanism which explains co-existence and overlapping of clinical symptomatology of CPH and TN, but it does not explain the genesis of the CPH-tic syndrome (21,22). That is why some authors suggest taking into account so-called helper parameters which are useful not only for mutual differentiation of TAC and tic syndrome (and therefore, the more precise diagnosis of the correlation of these conditions [TAC-tic]), but could also be the starting point for understanding pathophysiological differences and differences in clinical symptoms of TACs and TN (17). Some others state that brain predisposition that permits PH allows a peripheral stimulus in TN to be more readily expressed (23).

Painful syndromes of the head and face are common in patients with demyelinating diseases of the CNS. Studies devoted to examining more precise mechanisms of the occurrence of pain in these conditions, except associating the location of demyelinating plaque and the painful syndrome, did not give answers to questions about pathophysiology and evolution of painful syndromes in these patients (24). Similarly to our case report, there is a representation of a TAC-tic syndrome, where, as opposed to our case, cluster headache was combined with TN (Cluster-tic) as the initial manifestation of the clinically defined MS (20).

ConClusion

The authors think that the particularity of this report is the combination of otherwise individually rarer painful syndromes of the head and face (in relation to other headache syndromes), CPH and TN, which were the initial and only clinical manifestation of a demyelinating disease, defined as CIS. The authors think that this report represents a modest contribution to pathophysiological and clinical studying of CPH-tic syndrome and suggest that the revision of ICHD-III should also include the fact that a potential cause/primary disease for symptomatic TN could also be CIS (not only defined MS), along with the fulfillment of other existing criteria for symptomatic TN.

The correct and accurate diagnosis of TAC-tic syndrome is of crucial importance. It is based on the knowledge of ICHD-III criteria, because for each of these painful conditions there are defined therapeutic recommendations for terminating and preventing attacks. On the other hand, it is necessary to conduct additional neurovisualization examinations with the aim of discovering symptomatic cases, since it is usually impossible to perform causal therapy with symptomatic syndromes due to the nature of the primary pathological process. Therefore, the therapeutic approach, besides being symptomatic, could be fully effective in controlling CPH and TN.

Ethical Statement

The study was approved by the ethics committee of the Faculty of Medicine, University of Nis, and thus has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.
and its later amendments. The patient gave written informed consent for scientific use of her medical data.

**Statement of authorship**


**References**


