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Brief Communications

Two Cases of Hemicrania Continua–Trigeminal Neuralgia Syndrome: Expanding the Spectrum of Trigeminal Autonomic Cephalalgia-Tic (TAC-TIC) Syndrome

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Background.—Trigeminal neuralgia (TN) has been described in association with various primary headache disorders. So far, no case of TN has been reported in association with hemicrania continua (HC).

Case Report.—Here, we report two patients of hemicrania continua associated with TN (HC-tic syndrome). These patients had both headaches concurrently. Both patients responded to a combination of carbamazepine and indomethacin. The skipping or tapering of carbamazepine led to the recurrence of the neuralgic pain of TN. In the same way, the skipping of indomethacin resulted in the relapse of the pain, typical of HC.

Conclusion.—With these two cases of HC-tic syndrome, we suggest that TN has a special predilection for all types of TACs. Various speculations suggest that such associations are more than a simple coincidence, and both diseases may be causally interrelated. The identification of this association is important as both disorders may need separate drugs.

Key words: hemicrania continua, trigeminal neuralgia, indomethacin, trigeminal autonomic cephalalgias

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INTRODUCTION

The coexistence of two different primary headache disorders is not unusual. The coexistence of migraine and tension-type headache (TTH) is very common in the general population.[1] However, the coexistence of two rare primary headaches is scarce.[2] Trigeminal neuralgia (TN) has been reported with various other primary headaches such as migraine (migraine-tic syndrome),[3] cluster headache (cluster-tic syndrome),[4,5] and paroxysmal hemicrania (paroxysmal hemicrania-tic syndrome).[6–8] TN may also be associated with short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA).[8,9] TN may also coexist with multiple forms of trigeminal autonomic cephalalgias (TACs) in a single patient.[10] The diagnosis is important as both headaches may respond to two different classes of the drugs.[1] So far, no case of TN has been reported in an association with hemicrania continua

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This manuscript was not presented at any meeting or published, nor is being considered for publication elsewhere.

Consent

Written informed consent was taken from the patients to publish the report.

Conflict of Interest: None.

(HC). Herein, we are reporting two cases of hemicrania continua-tic syndrome. Written informed consent was obtained from both patients for publication of this report. The study did not need approval by our Institute Ethics Committee as per the local regulations for case reports.

CASE 1

A 51-year-old male was referred to the neurology department for the management of refractory TN. The patient was diagnosed as having left TN of maxillary division about 5 years previously. The patient's previous records and the clinical description were consistent with the diagnosis of TN of maxillary division. The pain was a sudden, lancinating type, very severe, lasting for a few seconds and aggravated by eating or chewing foods. His symptom was well controlled with carbamazepine (300 mg twice daily) until approximately one and a half years prior to presentation. The skipping of carbamazepine always led to the recurrence of neuralgic pain. However, for the last year, his pain had increased in frequency, duration, and even in severity despite taking carbamazepine. The dose of carbamazepine was increased up to 600 mg twice daily. However, the patient did not feel much improvement. Various combinations of drugs had been tried in the last 18 months including lamotrigine, gabapentin, pregabalin, baclofen, amitriptyline, tramadol. However, the patient did not feel much improvement with these drugs. However, his pain always became worse on omitting carbamazepine. Therefore, he continued to take carbamazepine.

On reviewing the history, we noted a change in the pattern of the headache for the last one and half years. Initially, he had only the paroxysm of severe lancinating pain lasting for a few seconds only. Now, he felt almost continuous mild to moderate intensity pain involving maxillary area, orbital, supraorbital, and parieto-temporal areas with episodic exacerbations. While some exacerbations were typical of his earlier attacks of TN lasting for a few seconds), other attacks were different. These attacks were of longer duration lasting from 5 minutes to 5–6 hours. During most of the exacerbations, the patient cried or felt agitation or showed pacing activity. On asking, the patient admitted having ipsilateral conjunctival injection, lacrimation and rhinorrhea, especially with longer duration. Neurological examinations and MRI brain including MR angiography were normal. Even three-dimensional fast imaging employing steady-state acquisition (3D FIESTA) sequence did not reveal any neurovascular contact between the trigeminal nerve and vessels.

We suspected a possibility of HC, and indomethacin was started at a dose of 25 mg three times a day. There was a marked response in the background headache and exacerbations within 24 hours. The dose was titrated to 50 mg t.i.d on the third day. He showed almost complete response at this dose. At this point, we stopped carbamazepine. However, there was recurrence of the pain. This reappearance of pain was typical of his earlier attacks of TN (sudden, very severe, for a few seconds only, lancinating type, localized only to the maxillary area, and was aggravated by eating or chewing foods). Carbamazepine was restarted and he showed a cessation of the pain. With a combination of indomethacin and carbamazepine, he had been almost symptom free. We made a diagnosis of both HC and TN. Over the next 12 months of follow-up, we attempted to taper both drugs separately on a few occasions. The patient could differentiate easily two different types of headaches on tapering of both drugs separately (ie, on tapering of indomethacin he felt pain like HC, while on tapering or skipping of carbamazepine, he felt neuralgic pain).

CASE 2

A 37-year-old man presented with a 15-month history of left-sided continuous mild to moderate head pain with superimposed exacerbations. The continuous background pain was maximal in the supraorbital, orbital, and infraorbital areas. The duration, frequency, and other characteristics of the exacerbations were highly variables. The exacerbations used to occur 2–30 times a day and the duration of exacerbations varied from a few seconds to a few hours (up to 6 hours). The characteristics of exacerbations varied from excruciating stabbing pain

to throbbing pain. The exacerbations were associated with ipsilateral conjunctival injection, tearing, lacrimation, and nasal congestion in about 25% of the attacks. During most of the exacerbations, the patient had been agitated and had shown pacing activity. The exacerbations were occasionally precipitated by chewing and eating. The patient never felt nausea, vomiting, photophobia, phonophobia, or any aura during the exacerbations. There were occasional nocturnal exacerbations. The headache never occurred on the right side. The patient was non-alcoholic and a non-smoker. Physical and neurological examinations were normal. Routine haematological and biochemical parameters were normal. Magnetic resonance imaging of the brain, orbit, and cervical spine did not reveal any abnormality. Three-dimensional FIESTA MRI did not show any neurovascular contact between the trigeminal nerve and vessels. Prior treatments with various drugs, such as propranolol, topiramate, sodium valproate, amitriptyline, gabapentin, pregabalin, ibuprofen, and naproxen produced minimal or no effect.

We suspected a possibility of HC as the patient fulfilled ICHD-3β criteria for HC. Indomethacin was started at a dose of 25 mg three times a day. There was marked response within 48 hours. The background headaches almost disappeared. There was a marked improvement even in the frequency of the exacerbations. The patient never had such improvement with any drug in the past. Indomethacin was gradually titrated up to 75 mg three times a day with further improvement in the exacerbations. However, the response was still not complete. There was no background headache. The patient noted exacerbations as very severe, lancinating, and only for few seconds. There were no 'longer duration' exacerbations. The pain was localized only to the maxillary area. A diagnosis of HC-partially responsive to indomethacin was made. However, based on the experience of Case 1, a possibility of co-existent TN was also suspected. A precipitation of some attacks by eating and chewing increases the possibility of associated TN. Carbamazepine was added to indomethacin. The patient showed almost complete improvement with the combination therapy of indomethacin (75 mg t.i.d) and carbamazepine (300 mg b.i.d). The dose of indomethacin was successfully reduced to 50 mg three times a day after 4 months. Further tapering of indomethacin led to the relapse of continuous headaches and exacerbations of longer duration attack. Tapering of carbamazepine was not successful and it always led to the relapse of the neuralgic pain. The patient was well controlled with this combination for the next 9-month follow-up.

DISCUSSION

ICHD-3β classifies TN in two broad groups: Classical TN and Painful trigeminal neuropathy. Classical TN is further classified into two subgroups: Classical TN, purely paroxysmal and Classical TN with concomitant persistent facial pain.[2] A possibility of classical TN with concomitant persistent facial pain was also considered in both patients. However, we considered a possibility of coexistent TN and HC in both patients for the following reasons: (i) the paroxysmal pain or exacerbations were of longer durations, lasting up to 6 hours. Classical TN patients with persistent pain has typical TN attacks of shorter duration, (ii) cranial autonomic features were frequent in both patients, (iii) pacing activity/restlessness was noted in both patients during exacerbations, (iv) both patients showed a complete response to the combination of carbamazepine and indomethacin, (v) there was the reappearance of background headache and long duration exacerbations on stopping indomethacin.

ICHD-3β recognizes association of TN with CH, PH, and SUNCT/SUNA in the 'note' section of these TACs. It suggests that patients should receive both diagnoses, as both disorders require separate treatments.[2] However, the ICHD-3β is silent about the association of TN with HC. To the best of our knowledge derived from a search of the literature, there is no case of coexistence of TN with HC. Based on the association of TN with other TACs, it would not be unreasonable to presume that TN may coexist even with HC.

Review of the literature suggests that in such cases, both headaches may occur either simultaneously or at different times.[4–9] Case 1 initially had the features consistent with TN and fulfilled the

ICHD-3β criteria of TN. Later, he developed HC as well. Thereafter, he had both headaches concurrently. Case 2 had features of both TN and HC on the same side since the onset. Both patients responded to the combination of indomethacin and carbamazepine. The skipping of indomethacin led to the recurrence of the headaches, typically of HC. In the same way, the skipping of carbamazepine resulted in the recurrence of TN. It suggests a possibility of both TN and HC at the same time. TN was typically located in the V2 division of the trigeminal nerve in both cases. The pain of HC was typically located in both ophthalmic and maxillary divisions.

The most important point in such combinations is whether two disorders are the part of a single spectrum or is it just a coincidence. It will be difficult to presume one or other hypothesis with just two cases. However, we can speculate to some extent if we consider other primary headaches associated with TN in the literature. Literature review suggests that TN is more likely to be associated with TACs. There are just three cases where TN was associated with headaches other than TACs (and all three cases were associated with migraine).[2] CH is the most common primary headache associated with TN. There are several case reports or case series of CH-tic syndrome.[4,5] The next common association of TN is with PH.[6–8] A few case reports of TN with SUNCT/SUNA have also been reported.[8,9] Therefore, we suggest that our cases of HC-tic syndrome are an extension of a bigger spectrum. All TACs may be associated with TN. Therefore, we can use trigeminal autonomic cephalalgia-tic (TAC-tic) syndrome as an umbrella term under which all other syndrome can be described.

The possibility of coincidence can be a simple explanation for such combination. However, the probability of simple coincidence is low because of the following reasons: (i) migraine is the most common headache in the clinical setting, while TTH is the most common headache in the general population. Therefore, with a simple coincidence rule, TN should more commonly occur with migraine or TTH. Very recently, Hinze et al[3] reported that there are just three cases of migraine-tic syndrome in the literature. Although a recent study indicates that migraine is a risk factor for the development of TN.[11] It would be interesting to know if it is associated with side-locked migraine or if there is any temporal relation between the development of TN and the development of migraine. (ii) The association of TN with all types of TACs (not with other headaches) suggests that this association is more than the chance, (iii) the lifetime prevalence of TN is 0.1–0.3%.[12] TN was noted in 4.5% of patients with CH in one cross-sectional study of CH patients.[5] It is more than the simple coincidence (iv) in such cases (TAC with tic), both headaches occur on the same symptomatic side. If it is simple coincidence, cases with opposite side involvement will be equally common. (v) Trigeminal nerve is the final pathway for both TN and TACs (trigeminal autonomic reflex is implicated for some features of TACs).

Pathophysiology.—Trigeminal neuralgia is usually caused by the demyelination of trigeminal nerve, which usually results from a compression by the overlying artery or vein. However, there are a number of causes of demyelination, including idiopathic. The demyelination leads to ectopic generation of impulses, which is followed by the ephaptic conduction to adjacent fibers. These impulses and ephaptic conduction generate electrical current like pain.[13] However, functional brain imaging (f-MRI) has shown increased activity in the spinal trigeminal nucleus, thalamus, somatosensory cortices, anterior cingulate cortex, insula, premotor/motor cortex, prefrontal areas, putamen, hippocampus, and brainstem after the stimulation of the cutaneous trigger zone in patients with TN. Even nonpainful stimulation of the trigger zone activated most of these structures.[14]

All TACs have a common pathophysiology. Both peripheral and central mechanisms have been suggested for the symptom complex of TACs. Available evidence suggests that posterior hypothalamus is crucial in the generation of headache attack in TACs.[15] A direct hypothalamic–trigeminal connection (trigemino-hypothalamic tract) has been demonstrated in rats[16] that controls the trigeminovascular-nociceptive pathways, including trigeminal autonomic reflex (TAR). Trigeminal autonomic reflex is the final pathway for all the TACs.[15]

Therefore, an overlap in the mechanisms of TACs and TN is apparent. So, it can be speculated that TACs may predispose to the development of TN and vice versa. The pain in TACs is mediated via trigeminal nerve (via trigeminovascular-nociceptive pathways, and TAR). We speculate that recurrent attacks of pain in TACs may induce demyelination (or other physiological abnormality) in the trigeminal nerve and it may be the reason for the development of TN in patients with TACs. In the same way, supraspinal facilitation in TN may lead to the development of one of the TACs. Both pathophysiological abnormalities may be present simultaneously and patients may have both symptoms concurrently.

A possible limitation to this work is that the clinical pattern and response to both drugs on two different types of headaches are highly suggestive of both disorders. However, the possibility of other disorders cannot be ruled out completely. A possibility of recall bias also remains with such observations.

CONCLUSION

With these two cases of HC-tic syndrome, we suggest that TN has a special predilection for all types of TACs. Both disorders may require separate drugs. There is a need to find out the pathophysiological mechanisms behind such association.

STATEMENT OF AUTHORSHIP

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