Secondary (Symptomatic) Trigeminal Autonomic Cephalalgia

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Abstract

Primary trigeminal autonomic cephalalgias (TACs) are uncommon group of headache disorders. These are defined and diagnosed by the criteria given by the International Classification of Headache Disorders 3β version. Over the past few decades, a number of secondary (symptomatic) cases have been described in the literature with headache features indistinguishable from primary TACs. Many structural and other pathologies have been found in these patients that can be causally related to the headaches. This review attempts to critically analyze the existing literature including the new cases published during 2015–2017.

Keywords: Cluster-like headache, secondary short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral headache attacks with autonomic features, secondary cluster headache, secondary hemicrania continua, secondary paroxysmal hemicrania, secondary trigeminal autonomic cephalalgias, symptomatic trigeminal autonomic cephalalgias

Introduction

Trigeminal autonomic cephalalgias (TACs), the term coined by Goadsby and Lipton, is now considered a broad rubric under which four types of primary headache disorders are included (Group 3 in International Classification of Headache Disorders 3β version [ICHD3β]).1,2 These include cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral headache attacks with autonomic features (SUNA) (under short-lasting unilateral neuralgiform headache attacks), and hemicrania continua (HC). Although considered uncommon, these headaches are one of the worst pain syndromes known to humankind.

As the nosology and the classification of TACs evolved over the years, many secondary cases were described with an underlying structural pathology. Sometimes, headache features in these secondary TACs were undistinguishable from those with primary TACs, and sometimes, they only apparently mimicked the primary TACs and their secondary nature was belied due to the presence of atypical features. Some excellent reviews are available detailing these cases from 1975 to 2015.3–8 Some reviews focused only of secondary CH,4,7 CH being the most common of TACs subtypes. Secondary HC has been included only in one review as it was included in TACs group only in 2013.[8] The purpose of the present article is to critically review the concept of secondary TACs and analyze the new secondary TACs and TACs-like cases reported from February 2015 to July 2017.

Concept of Secondary Headache in the Context of Secondary Trigeminal Autonomic Cephalalgias

For the diagnosis of secondary headache due to a disorder, the causative disorder must be known to cause headache. When new headache occurs in close temporal relationship with such a disorder, it is diagnosed as a secondary headache even though the phenotype is of a primary headache disorder.[2] Although close temporal relationship suggests causation, ICHD3β requires fulfillment of at least one or more of the following conditions, namely worsening and/or improvement of headache with worsening and/or improvement of the presumed causative disorder; headache having characteristics typical of a causative disorder (for example, thunderclap headache for subarachnoid hemorrhage); and existence of other evidence of causation (for example, a biochemical marker-like erythrocyte...
sedimentation rate [ESR] for giant cell arteritis [GCA] or location of headache).\textsuperscript{[3]} Two other situations may also exist. When a preexisting primary headache becomes chronic or becomes significantly worse (more than twofold increase in attack frequency and/or severity) in close temporal relationship with a causative disorder, both the primary and secondary diagnoses are recommended. In the context of TACs, it has been difficult to establish causality with the underlying pathology in many cases. This is because of many reasons. First, because of retrospective nature of most of the case reports, temporal relationship was difficult to establish. Further, imaging was done in a cross-sectional manner. Detection of an abnormality on magnetic resonance imaging (MRI) in a patient at the time of presentation or during one point in patient’s subsequent follow-up does not necessarily provide definitive clues about its onset or its progression. A typical example is the presence of pituitary adenoma in many TAC patients. Are these incidental or causal? As pituitary micro-adenomas and macro-adenomas can be found in as high as 1% and 0.2%, respectively, of the population who are asymptomatic,\textsuperscript{[9]} detection of pituitary tumor in a case of TACs does not necessarily point toward causality. Most of the case reports relied on the fact that headache resolved after the treatment of underlying pathology although time of follow-up was not stated in many cases. There may be other reasons for the response such as natural fluctuations or placebo effect. Many cases of secondary CH had responded to the existent treatment (as for the primary CH) as well. Many patients of secondary PH and HC have responded well to indomethacin before their response to the treatment of underlying pathology. Therefore, it is difficult to hold onto this criterion alone for demonstrating causality. To obviate this difficulty, some authors have divided these cases into three groups, namely probable secondary, possible secondary, and unknown.\textsuperscript{[9]}

### Overview of the Previously Published Reports

The previous reviews are summarized in Table 1. Although these reviews had varying search modalities and inclusion and exclusion criteria, certain general points which emerged from them are worth noting.

1. Nearly half of the patients had “typical” features of TACs fulfilling ICHD2 and/or ICHD3β criteria despite having a structural intracranial or extracranial pathology to account for their headaches. Hence, it has been suggested that neuroimaging should be done in all patients of TACs.\textsuperscript{[3,6,8]} Although this appears appealing, some authors have argued that definitive recommendations for neuroimaging cannot be generalized to all TAC patients because of retrospective nature of the case reports and small number of cases.\textsuperscript{[4,5,7]} As mentioned previously, even if a structural pathology is found, cause-and-effect relationship is difficult to establish in many cases. There are no population-based studies available to throw light on this issue. On the other hand, since many of the etiologies for secondary TACs are potentially serious, others have argued that neuroimaging should be routinely offered to such patients. Fortunately, TACs are relatively uncommon (as compared to migraine and tension-type headache), and hence, the economic burden for such investigations may not be much of a concern although “incidentalomas” picked up during routine neuroimaging may be potentially confusing.

2. Nearly half of the secondary TAC patients also had “atypical features,” sometimes very obvious, and sometimes too trivial to attract attention of the clinicians. All TAC patients must therefore be carefully scrutinized for the presence of any “atypical” features and be subjected to investigations if any of these are detected. These atypical features may be present at the time of presentation or may develop subsequently. High index of suspicion must therefore be kept for any atypicality.

3. Certain red flags have been identified which must prompt for further investigations. These include older age at onset, abnormal general or neurological examination, attack-related features not fulfilling ICHD criteria, namely duration, frequency, and localization, and unresponsiveness to treatment.

4. Many reports also describe patients with TAC-like headaches which only superficially exhibit TAC features. Their onset, duration, frequency, and presence of additional neurological symptoms and signs clearly mark them as mere mimickers rather than true TACs. For example, Mainardi et al.\textsuperscript{[10]} identified 156 cluster-like headaches from 1975 to 2008. Eighty were excluded because of inadequate information. Of the remaining 76, only 38 (50%) fulfilled the diagnostic criteria of CH as per the ICHD2.

5. About one-third of secondary TAC patients had “episodic pattern” of headaches. Hence, contrary to common belief, even episodic TACs patients can have a secondary cause and should be considered for imaging.

6. Overall, the reported occurrence of secondary TACs has been low. However, exact proportion is difficult to ascertain as the reported cases are in the form of case reports and small series, and none of them reported the number of primary TACs cases seen during the same period. Furthermore, lower detection could be due to the fact that previously many of these patients were not imaged. There is a trend toward greater reporting of secondary TACs over the years.

7. Intracranial tumors are probably the most common causes for secondary TACs, although in the some recent reviews their proportion has decreased (around 30% as compared to 50% in earlier reviews).\textsuperscript{[7,8]} Among the tumors, the occurrence of pituitary tumors is particularly high. Most of these pituitary tumors are functioning tumors and removal/medical treatment of these has resolved headaches in most cases for at least a certain period in follow-up, thereby lending credence to the supposition of causal relationship.

8. Another important cause of secondary TACs is vascular abnormalities mainly in the form of dissections and
9. Response to treatment has been a tricky issue in secondary TACs. In many reports, the casual relationship with the detected pathology was demonstrated by showing the resolution of the headache by an intervention aimed at the pathology. However, other possibilities may exist such as spontaneous resolution of an episodic disease (intervention being coincidental), natural fluctuations in disease severity, or placebo effect. Further, a large number of patients of secondary TACs have responded to the standard existent treatment aimed at the primary disorder. Hence, it is difficult to judge whether the effect produced by an intervention was indeed significant. Only long-term follow-up could answer that. Unfortunately, many reports lacked the details of long-term follow-up after intervention.

10. There are increasing case reports of the presence of neurovascular conflict in SUNCT/SUNA, and many such patients had dramatic improvement in their headaches following microvascular decompression (MVD). Favoni et al.\textsuperscript{[11]} in a review identified 222 cases of SUNCT/SUNA and found neurovascular conflicts in 37 (16.7%). Sixteen patients underwent MVD and 75% reported complete pain relief. While some authors have considered cases of SUNCT/SUNA with vascular loop on the symptomatic

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**Table 1: Summary of the reviews on symptomatic trigeminal autonomic cephalalgias (1975-2015)**

| Number | Author               | Journal/year | Title                                              | Period of search | Number of cases | Comments | Etiology                                                                 |
|--------|----------------------|--------------|----------------------------------------------------|------------------|-----------------|----------|--------------------------------------------------------------------------|
| 1      | Favier et al.\textsuperscript{[6]} | Arch Neurol., 2007 | Trigeminal autonomic cephalalgias because of structural lesions: A review of 31 cases | January 2001-December 2005 | 31              | 27 previously described cases and 4 cases of their own; 27 cases were excluded. There were 16 cases of CH/PH; 1 cluster tic; 4 SUNCT and rest 10 had atypical TACs | 8 had vascular lesions, 16 had cerebral tumors (11 pituitary tumors; 10 functioning) and rest miscellaneous lesions |
| 2      | Favier et al.\textsuperscript{[6]} | Curr Pain Headache Rep. 2008 | Cluster headache: To scan or not to scan | 2001-2008 | 23 (21+2) | 2 more CH cases were added | Both had tumors; 1 had pituitary tumor |
| 3      | Cittadini and Matharu\textsuperscript{[7]} | The Neurologist 2009 | Symptomatic trigeminal autonomic cephalalgias | 1975-May 2007 | 40              | 24 patients of CH. Of these, 12 had typical and 12 had atypical features; 1 had CH-Tic. 50% responded to abortive treatment; 3 patients with PH; All had atypical features; 10 cases of SUNCT; 5 had atypical features | 12 (50%) of CH patients had tumors; 7/12 had pituitary tumors (6 functioning) and 33% vascular lesions. All PH patients had mass lesions; 2 had functioning pituitary adenomas. All PH patients had absolute response to indomethacin. All SUNCT patients had mass lesions; 7 had pituitary adenomas (5 functioning) |
| 4      | Wilbrink et al.\textsuperscript{[8]} | Curr Opin Neurol. 2009 | Neuroimaging in trigeminal autonomic cephalalgias: when, how, and of what? | January 2001-2008 | 56              | (33 from reviews of 1 and 2) and 23 additional cases. Described TACs and TACs-like syndromes | 27 had tumors (more than 50% were pituitary tumors), 22 had vascular lesions and the rest miscellaneous causes |
| 5      | Edvardsson\textsuperscript{[7]} | Springer Plus 2014 | Symptomatic cluster headache: A review of 63 cases | From 1993 to May 2013 | 63              | Focused only on symptomatic CH | 28 patients had vascular lesions (11 had dissections); 25 had tumors (10 pituitary tumors); 48% had typical presentations while 52% had atypical presentations |
| 6      | de Coo et al.\textsuperscript{[9]} | Curr Pain Headache Rep 2015 | Symptomatic trigeminal autonomic cephalalgias | February 2009-January 2015 | 53              | Updated series from review 4; 53 typical cases were identified; 19 cases with CH, no cases with paroxysmal hemicrania, 6 cases with hemicrania continua, and 28 cases with SUNCT/SUNA; classified as probable, possible and unknown | 16 of the 53 cases had tumors (mainly pituitary tumors); more than 40% of patients with SUNCT/SUNA had neurovascular conflict and that most experienced spectacular improvement after surgical decompression |

TACs=Trigeminal autonomic cephalalgias, CH=Cluster headache, PH=Paroxysmal hemicranias, SUNCT=Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, SUNA=Short-lasting unilateral headache attacks with autonomic features.
side as secondary, there is no mention in ICHD3β about the nosology of this entity. Interestingly, cases of trigeminal neuralgia (TN) with neurovascular conflict are considered as “classical” in ICHD3β.

**NEW CASES OF SECONDARY TRIGEMINAL AUTONOMIC CEPHALALGIAS (JANUARY 2015–JULY 2017)**

**Secondary cluster headache**

We found 10 new reports for secondary CH and CH-like headaches [Table 2].

**Tumors**

De Pue et al.\(^{[12]}\) described a 47-year-old male who suffered from primary right-sided chronic CH for 12 years, never attack-free for more than 1 month. His initial MRI scan was normal. Subsequently, the patient developed continuous interictal pain at the same site, and repeat MRI showed a cystic pituitary lesion consistent with a Rathke’s cleft cyst or cystic adenoma with high prolactin levels. On cabergoline, his headaches were completely resolved.

Robin et al.\(^{[13]}\) described a very interesting case of CH being “cured” by a glioblastoma. A 49-year-old male had refractory right chronic CH (CCH) for 4 years who failed various preventive treatments, blocks, and occipital nerve stimulation. He refused deep brain stimulation. Subsequently, he developed fresh neurological symptoms in the form of dizziness, ataxia, and hemiparesis. However, interestingly, it was found that 2–3 weeks before the onset of these neurological symptoms, his chronic headaches had stopped. Glioblastoma multiforme was detected involving right cingulate gyrus. Following operation, he only had few mild attacks for 1½ months which completely resolved thereafter till he succumbed to his illness 1 year later.

Escuti\(^{[14]}\) described a case of 50-year-old man who 9 years back had generalized headaches to an occipital lipoma, resection of which provided him with considerable albeit not full relief. Following this, for the past 2 years, the patient started having CH-like attacks. Repeat imaging showed regrowth of the lipoma at C1–C2 level. Headaches were relieved by sumatriptan injections. The lipoma was not operated and the patient reported decrease in attacks following significant weight loss.

**Vascular**

Eswaradass et al.\(^{[15]}\) reported a case of 44-year-old male patient who presented with episodic right-sided headaches for 1 month, 1–3 times a day with narrowing of palpebral fissure and mild lacrimation. The patient had restlessness and agitation during the episodes. There was no significant response to analgesics and 100% oxygen. MRI brain was normal. Digital subtraction angiography revealed right indirect carotid cavernous fistula. Following endovascular embolization, the patient had complete relief in headache.

Bellamio et al.\(^{[16]}\) reported two cases of secondary CH due to vascular etiology. First was a 71-year-old male who had features of left-sided episodic cluster for the past 20 years. He had been taking various preventives with moderate relief. An MRI scan at some point in his illness showed a left pontine cavernous angioma, which was considered an incidental finding. Then, few years later, his headache type changed suddenly from episodic CH (ECH) to CCH without any response to preventive medications. Repeat MRI showed increase in size of the cavernous angioma. Surgery resolved his headaches completely, and he remained headache-free till 6 years of his last follow-up. The second patient was a 29-year-old male with right-sided CH. His first cluster period lasted for 2 weeks with attacks occurring at fixed times of the day with accompanied by autonomic symptoms. Three months later, he presented with the next cluster period of 1 month with similar features. After 1 month, he developed fever, meningeal irritation, and features of intracranial hypertension. His MRI showed left external jugular vein thrombosis climbing up to sigmoid sinus. Treatment with warfarin and acetazolamide successfully resolved his headache. He was pain-free at 1 year.

de Coo et al.\(^{[17]}\) reported a patient with cluster-Tic syndrome. Initially, the patient had only TN. After 6 months, she started developing redness and tearing. She did not respond to indomethacin. One year later, she developed CH attacks occurring up to four per day, each lasting 30–90 m. Previous two MRIs were reported as normal. However, review of the last MRI showed compression of the left trigeminal nerve by the petrosal vein. Vascular decompression abolished the TN and decreased CH attacks although they did not disappear completely.

Semnic et al.\(^{[18]}\) reported a case of 49-year-old male with features superficially resembling left-sided ECH. However, there were no autonomic symptoms associated with headache attacks and restlessness was not mentioned. Furthermore, mild numbness and hyperalgesia of the affected area were present. Similar headache occurred 3 years back for 45 days with complete resolution of symptoms. MRI showed segmental cavernous carotid ectasia. Treatment details were not mentioned.

**Miscellaneous**

Kao and Hsu\(^{[19]}\) reported a case of 26-year-old male who presented with a thunderclap-like headache involving right forehead precipitated by cough. Subsequently, the headache persisted for 2 weeks in episodic form lasting 2–3 h, 3–4 times/day and got precipitated by cough and exertion. It was associated with rhinorrhea and tearing from right eye. Subsequently, he developed persistent anhidrosis of his right face and trunk. In addition, he developed persistent numbness of right half of the body. MRI showed caudal descent of cerebellar tonsils compression of posterolateral aspect of the right cervical spinal cord and syringomyelia. His headaches resolved completely after decompression surgery.

Pelikan et al.\(^{[20]}\) reported a case of 42-year-old female with sudden-onset left-sided headache with ipsilateral autonomic symptoms. She visited the emergency department (ED)
Table 2: Secondary cluster headache and cluster headache-like headaches (February 2015 to June 2017)

| Number | Author (year) | Age/sex | Headache phenotype | Laterality of headache | Duration of headache diagnosis* | Atypical features | Underlying pathology | Laterality of the pathology | Treatment before the diagnosis of secondary pathology | Treatment after the diagnosis of secondary pathology | Outcome/ follow-up duration after the treatment of the pathology |
|--------|---------------|---------|-------------------|-----------------------|-------------------------------|------------------|---------------------|------------------------|--------------------------------|--------------------------------|--------------------------------------------------|
| 1      | Bellamio et al. (2017)[16] | 71/male | ECH-CCH | Left | 20 years | Sudden change of ECH to CCH | Pontine cavernous angioma | Left | ECH responded to conventional treatment; CCH did not respond | Surgery | Headache resolved completely/6 years |
| 2      | Bellamio et al. (2017)[16] | 29/male | ECH | Right | 4 months | Sudden change in headache character; fluctuating vision loss; meningeal irritation, fever, raised ICP | External jugular vein thrombosis | Left | Not mentioned | Acetazolamide and warfarin | Headache resolved completely/1 year |
| 3      | de Coo et al. (2017)[17] | 41/female | Cluster-Tic | Left | 6 years | Initially, attacks of TN occurred only upon standing from sitting | Petrosal venous compression of trigeminal nerve | Left | CH attacks responded to oxygen; verapamil had not effect | Surgery | TN resolved completely. CH frequency and intensity decreased/ follow-up period not mentioned |
| 4      | De Pue et al. (2016)[12] | 47/male | CCH | Right | 12 years | Change in headache characteristic; continuous interictal headache | Rathke’s cleft cyst/cystic adenoma (prolactinoma) | Right | Relief with sumatriptan injections; modest response with verapamil | Cabergoline | CCH stopped; 6 months later probable SUNA evolved/1.5 years |
| 5      | Pelikan et al. (2016)[20] | 42/female | ECH | Left | 4 months | Numbness in lip, face, and tongue; ataxia and clumsiness of left hand | MS; Demyelinating plaques; one large plaque in right centrum semiovale | Right | Responded to dihydroergotamine | Dimethyl fumarate | Headache resolved completely/1 year |
| 6      | Escuti (2015)[14] | 50/male | ECH | Right | 2 years | Previously operated for occipital lipoma for generalize headaches | Regrowth of lipoma at C1-C2 level | Left | Relief with sumatriptan injections | No further surgery offered | Headache decreased in severity on weight reduction/ spontaneously |
| 7      | Kao and Hsu (2015)[19] | 26/male | ECH | Right | 2 weeks | Thunderclap type presentation followed by episodic headaches; precipitated by cough, exertion; sensory loss; anhidrosis | Type 1 Chiari malformation | Right cord compression | Not mentioned | Decompression | Complete relief in headache/few days |
| 8      | Robin et al. (2015)[13] | 49/male | ECH-CCH | Right | 4 years | Change of headache character to CDH; 2-3 weeks prior had dizziness, ataxia and hemiparesis | GBM involving cingulated gyrus | Right | Failed standard treatment, blocks and ONS; refused DBS | Headache subsided 2-3 weeks before development of fresh neurological symptoms. Resective surgery performed | Headache disappeared completely following 6 months of surgery |

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where she was given dihydroergotamine and her headaches resolved. However, she developed numbness on the left side of lips and facial numbness in the mandibular and maxillary areas. Two months later, other neurological symptoms such as hand clumsiness and gait ataxia developed. She continued to have similar headache attacks. Her MRI showed multiple demyelinating plaques including a large plaque in the right centrum semiovale. She was started on dimethyl fumarate and her headaches completely resolved.

**Secondary paroxysmal hemicrania**

We found three new reports for secondary PH and PH-like headaches [Table 3].

Ljubisavljevic et al.\(^{[21]}\) reported a 40-year-old female patient who presented with two types of right facial pain for 2 years. The first type was TN consisting of paroxysm of attacks in V2/V3 distribution and was triggered by various stimuli; the second one was throbbing orbital and frontal pain with ipsilateral autonomic symptoms such as conjunctival injection, lacrimation, and aural fullness. This pain lasted most often between 15 and 20 m. Thus, a diagnosis of CPH-Tic syndrome was considered. On MRI, there were multiple hyperintense paraventricular lesion and hyperintense lesion in the right trigeminal main sensory nucleus and root inlet. All were hypointense on T1 and did not show any enhancement on contrast. Thus, a diagnosis of clinically isolated syndrome presenting as CPH-Tic syndrome was made. Headaches were completely relieved by indomethacin and lamotrigine at 6 months.

Choi et al.\(^{[22]}\) described a 43-year-old male presenting with severe paroxysmal left periocular and frontal headaches 10–12 times/day lasting 10–15 m with ipsilateral conjunctival congestion and lacrimation for 1 year. Initial MRI was normal. The patient did not get relief with indomethacin, various other drugs, and occipital and sphenopalatine ganglion blocks. A repeat MRI 1 year later showed left superior oblique mass. On further evaluation, it was found to be metastatic leiomyosarcoma arising from a primary focus in the right thigh. The patient had complete relief of his headache following gamma knife surgery of his orbital leiomyosarcoma.

Taga et al.\(^{[23]}\) reported isolated attacks of headache resembling PH after tadalafil and sildenafil (phosphodiesterase-5 inhibitors) administration in a 35-year-old man. The patient was a case of Alcock syndrome (pudendal nerve entrapment) and had erectile dysfunction. Indomethacin completely relieved these headaches triggered by tadalafil and sildenafil.

**Secondary short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral headache attacks with autonomic features**

We found 10 new reports for secondary SUNCT/SUNA and SUNCT/SUNA-like headaches [Table 4]. We excluded the case reports with neurovascular conflict.

**Vascular**

Lambru et al.\(^{[24]}\) described a case of 58-year-old male with right-sided chronic SUNCT and TN for 16 years which
| Number | Author(s) (year) | Age/sex | Headache phenotype | Laterality of headache | Duration of headache diagnosis* | Atypical features | Underlying pathology | Latetality of the pathology | Treatment before the diagnosis of secondary pathology | Treatment after the diagnosis of secondary pathology | Outcome and follow-up duration after the treatment of the pathology |
|--------|-----------------|---------|-------------------|------------------------|-------------------------------|-----------------|------------------|------------------------|--------------------------------|--------------------------------|---------------------------------------------------------------|
| 1      | Ljubisavljevic et al. (2017)[21] | 40/ female | CPH-Tic | Right | 2 years | Hypoesthesia in the region of right maxillary and mandibular nerve | Multiple demyelinating lesions especially at right trigeminal main sensory nucleus and root inlet and right corticospinal tract at the medulla oblongata presenting as CIS | Right | Partial response to carbamazepine and amitriptyline | Indomethacin and lamotrigine | Complete pain relief at 6 months |
| 2      | Choi et al. (2017)[22] | 43/ male | CPH | Left | 1 year | None | Orbital (left superior oblique) metastatic leiomyosarcoma arising from the thigh | Left | No response to indomethacin, other drugs and SPG and occipital blocks | Gamma knife | Complete pain relief at 3 months |
| 3      | Taga et al. (2017)[23] | 35/ male | EPH | Right | Not mentioned | Always provoked by tadalafil, sildenafil intake | Phosphodiesterase inhibitors administration | Not applicable | No response to analgesics | Indomethacin/ not mentioned | Complete relief |

CIS=Clinically isolated syndrome, CPH=Chronic paroxysmal hemicranias, SPG=Sphenopalatine ganglion, EPH=Episodic primary headache, *At the time of diagnosis of secondary pathology

Miscellaneous

Bark et al.[24] described a 33-year-old female who had an episode of pulsatile headache in 2010 from lamotrigine intake. Her headache was associated with autonomic features and left-sided headache. She had partial response to tadalafil, sildenafil, and gabapentin.

Gošmen et al.[25] described a case of 64-year-old male presented with left SUNCT-like attacks. There was a history of self-limiting similar attacks 2 years back. His MRI showed right pontine capillary telangiectasia. He had these attacks 20–30 times a day, lasting 5–10 min. He had these attacks 20–30 times a day, lasting 5–10 min.

Gošmen et al.[25] reported a case of 43-year-old male with left-sided headache following ingestion of coffee and alcohol intake, physical or emotional stress, insomnia, and sexual activity. He had only partial response to indomethacin, gabapentin, and lamotrigine.

Coermann et al.[26] reported a case of 43-year-old male with left-sided headache following ingestion of coffee and alcohol intake. He had these attacks 20–30 times a day, lasting 5–10 min. He had these attacks 20–30 times a day, lasting 5–10 min.

Jin et al.[27] reported a case of 43-year-old male with left SUNCT attacks. He sought treatment after 14 days.

Korkmaz et al.[28] reported a case of 64-year-old male presented with left SUNCT. He had a history of self-limiting similar attacks 2 years back. His MRI showed right pontine capillary telangiectasia. He had these attacks 20–30 times a day, lasting 5–10 min. He had these attacks 20–30 times a day, lasting 5–10 min.

Lapounova et al.[29] described a case of 15-year-old male who presented with sporadic SUNCT-like attacks 2 years after the onset of MEN1. His MRI showed right pontine capillary telangiectasia. He had these attacks 20–30 times a day, lasting 5–10 min. He had these attacks 20–30 times a day, lasting 5–10 min. He had these attacks 20–30 times a day, lasting 5–10 min. He had these attacks 20–30 times a day, lasting 5–10 min.

Nagel et al.[30] reported a case of 15-year-old male with SUNCT headaches who responded to bilateral greater occipital and left supraorbital nerve block with methylprednisolone and lidocaine.
| Number | Author (year)          | Age/sex | Headache phenotype | Laterality of headache | Duration of headache diagnosis* | Atypical features                                      | Underlying pathology                                                                 | Laterality of the pathology | Treatment of headache before the diagnosis of secondary pathology | Treatment after the diagnosis of secondary pathology | Outcome and follow-up duration after the treatment of the pathology |
|--------|------------------------|---------|--------------------|------------------------|--------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 1      | Lambru et al. (2017)   | 58/     | Chronic SUNCT and TN | Right                  | 16 years (started 3 weeks after stroke) | None                                                   | Infarct in right dorsolateral medulla due to VA dissection; bilateral neurovascular conflict without any compression, indentation or distortion | Right                       | Multiple drugs                                              | Carbamazepine and gabapentin; could not tolerate lamotrigine | 40% relief                                                                                     |
| 2      | Liapounova et al. (2017) | 15/     | Episodic SUNCT     | Right                  | Diagnosed after admission in ED; history of self-limiting previous episode 2 years back | Mild hyperesthesia right side of the face               | Right pontine capillary telangiectasia and developmental venous anomaly           | Right                       | Not applicable                                             | Initially, partial response to oxygen; later carbamazepine | Complete response; 1 year                                                                 |
| 3      | Mangaraj et al. (2017) | 22/     | Episodic SUNCT     | Left                   | 10 years                           | Secondary amenorrhea, galactorrhea                      | Macroprolactinoma                                                                  | Whole of pituitary with suprasellar extension | Not mentioned                                           | Cabergoline; pituitary mass also decreased on drug | Complete response; 1 year                                                                 |
| 4      | Mathew et al. (2016)   | 58/     | Episodic SUNCT     | Right                  | 1 year                             | None                                                   | Herpes zoster in V1 (previous)                                                      | Right                       | Not applicable                                             | Pregabalin and lamotrigine                                          | Complete relief; 5 years                                                                 |
| 5      | Mathew et al. (2016)   | 60/     | Episodic SUNCT     | Left                   | 1 month                            | None                                                   | Herpes zoster in V1 (previous)                                                      | Left                        | Not applicable                                             | Pregabalin                                             | Complete relief; 3 months                                                                 |
| 6      | Nagel et al. (2016)    | 47/     | Episodic SUNCT     | Left                   | 1 month                            | None                                                   | Herpes zoster in V1 (acute infection)                                                 | Left                        | Not applicable                                             | Repeat course of valacyclovir; Lamotrigine                        | Complete relief; 2 years                                                                 |
| 7      | Berk and Silberstein (2016) | 33/     | Episodic SUNCT     | Right                  | 1 month                            | None                                                   | Postradiation to a pituitary adenoma invading cavernous carotid artery              | Right                       | Not applicable                                             | Lamotrigine                                            | Partial response                                                                 |
| 8      | Jin et al. (2016)      | 64/     | Episodic SUNCT     | Left                   | 13 days                            | None                                                   | Infarct in left dorsolateral medulla; left VA occluded                              | Left                        | Not applicable                                             | No drug given                                           | Spontaneous resolution of headache within 14 days; 5 months                                                                 |

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Secondary (symptomatic) trigeminal autonomic cephalalgia

Table 4: Contd...

| Number | Author (year) | Age/sex | Headache phenotype | Duration of headache diagnosis* | Atypical features | Underlying pathology | Laterality of the pathology | Treatment of headache before the diagnosis of secondary pathology | Treatment after the diagnosis of secondary pathology | Outcome and follow-up duration after the treatment of the pathology |
|--------|---------------|---------|--------------------|--------------------------------|------------------|----------------------|--------------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|
| 9      | Rojas-Ramirez (2016)[31] | 57/female | SUNCT | 2 years | Palpation of left trapezius resulted in attacks; no other triggers | Head and neck trauma | None | None | Lamotrigine (could not tolerate); gabapentin and melatonin | Significant response; 2 years |
| 10     | Gocmen et al. (2015)[32] | 43/male | SUNCT | 1 month | History of lifting heavy objects just before the start of the headache attacks; transient left-sided sixth nerve palsy | Pontine capillary telangiectasia | Left | Not mentioned | Partial response to indomethacin; followed by bilateral greater occipital and left supraorbital nerve block with methylprednisolone and lidocaine | Complete response; 8 months |

SUNCT=Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, TN=Trigeminal neuralgia, VA=Vertebral artery, ED=Emergency department, *At the time of diagnosis of secondary pathology

Vascular

Brilla et al. [33] described five cases of HC-like headaches following cervical artery dissection, in three cases with specific indomethacin response. In two cases, comorbidity of fibromuscular dysplasia was noted. However, all cases had atypical features for HC. The first case was a 50-year-old Caucasian female with subacute onset of headaches over the span of a day, initially in the left ear and occiput, then behind the left eye. Her magnetic resonance angiography (MRA) showed a left internal carotid artery (ICA) dissection with 200 mg/day. She was treated with warfarin. The second case was a 38-year-old man with a 4-day history of right-sided temporo-orbital headache of moderate-to-severe intensity. She had complete relief with indomethacin. The third case was a 44-year-old physician who noted subacute onset of headaches over the scalp in the temporal region. She complained of hypersensitivity of the scalp. She responded to indomethacin. Ultrasound and later MRI showed a left internal carotid artery (ICA) dissection with 200 mg/day.
| Number | Author (year) | Age/sex | Headache phenotype | Laterality of headache | Duration of headache diagnosis* | Atypical features | Underlying pathology | Laterality of the pathology | Treatment before the diagnosis of secondary pathology | Treatment | Outcome and follow-up duration after the treatment of the pathology |
|--------|---------------|---------|--------------------|------------------------|---------------------------------|------------------|----------------------|---------------------------|---------------------------------|-----------|---------------------------------------------------------------|
| 1      | Brilla et al. (2017) | 50/female | HC                 | Left                   | Few days                        | Pain in left ear and occiput to begin with | Carotid dissection with co-morbid FMD | Left                      | Gabapentin/ NSAIDs            | Indomethacin; later withdrawn due to FMD-related renal involvement | Complete relief while on indomethacin/1 year |
| 2      | Brilla et al. (2017) | 44/male | Probable HC        | Right                  | Headache started later          | Presented initially with only Horner’s; headache started 2 days later | Carotid dissection | Right                      | Warfarin                       | Indomethacin after 2 days | Complete relief; indomethacin stopped after 3 months |
| 3      | Brilla et al. (2017) | 47/female | Probable HC        | Right                  | Headache started later          | Presented initially with only miosis and intermittent ptosis; headache started 1 day later | FMD, carotid dissection, ACOM aneurysm | Right                      | NA                             | Stenting and clipping | Headache resolved in 6 months with analgesics |
| 4      | Brilla et al. (2017) | 42/male | Probable HC        | Left                   | 3 weeks                         | Headache started after lifting heavyweight | Occlusion of the ICA, with intramural hematoma indicating dissection | Left                      | NA                             | Methylprednisolone and acetaminophen | Headache relief in 4 weeks |
| 5      | Russo et al. (2017) | 62/male | HC                 | Left                   | 1 year                          | Initially raised ESR; after 1 year, left 6th nerve palsy | Widespread but asymmetrical pachymeningeal thickening (more prominent in the left side) and left transverse and sigmoid cerebral sinus thrombosis | Left                      | Steroids, indotest followed by oral indomethacin | Methylprednisolone and enoxaparin | Headache resolved/2 weeks |
| 6      | Mainardi et al. (2017) | 66/male | Probable HC        | Right                   | 4 months                        | None                           | TNP                               | NA                         | None                           | Withdrawal of TNP | Relief in headache within 24 h Headache gradually ceased |
| 7      | Zhang et al. (2017) | 31/male | HC                 | Left                    | 4 months                        | Left 6th nerve palsy on follow up after 1 month | Nasopharyngeal carcinoma | Left                      | Complete response to indomethacin | Chemoradiotherapy | Headache resolved/2 weeks |
| 8      | Alim-Marvasti et al. (2016) | 40/male | Left to right | 3 months               | Abnormal optic disc appearances and lack of absolute response to indomethacin | Recurrent alternating scleritis | Left > right | NSAIDs, triptans, partial response to indomethacin | Prednisolone | Complete relief; follow-up not mentioned |
| 9      | Gantenbein et al. (2015) | 44/male | Probable HC | Left                   | 3 months                        | Started 3 months following cranial schwannoma | Operated for vestibular schwannoma | Left                      | NSAIDs            | Indomethacin | Complete relief in headache; 4 months |

*Contd...
| Number | Author (year) | Laterality | Laterality of the headache | Laterality of the diagnosis | Underlying pathology | Treatment before the diagnosis | Treatment | Follow-up duration after the treatment of the pathology | Outcome and laterality | Atypical features |
|--------|---------------|------------|----------------------------|---------------------------|----------------------|-----------------------------|-----------|--------------------------------------------------------|----------------------|-----------------|
| 10     | Gantenbein et al. (2015) | Left       | Right                      | Left                      | Sided selective amygdalohippocampectomy with extirpation of temporomesial cortex | Gabapentin    | Indomethacin, gabapentin                              | Complete relief in headache with indomethacin; could not tolerate gabapentin | Partial response to Gabapentin | Severe exacerbations daily, lasting 45–60 min, accompanied by intense squinting of the left eye. | Major response to Gabapentin. |
| 11     | Gantenbein et al. (2015) | Right      | Right                      | Right                     | Operated for vestibular schwannoma | Gabapentin    | Indomethacin, gabapentin                              | Complete relief in headache with indomethacin; could not tolerate gabapentin | Partial response to Gabapentin | Severe exacerbations daily, lasting 45–60 min, accompanied by intense squinting of the left eye. | Major response to Gabapentin. |

**Tumor**

Zhang et al.\(^{[34]}\) described a 31-year-old man presented with a 4-month history of continuous left temporal pain with frequent exacerbations. The exacerbations were associated with ipsilateral conjunctival injection and a sense of restlessness. The pain entirely resolved with indomethacin. His initial MRI had very subtle changes and nasopharyngoscopy was noncontributory. However, a repeat contrast MRI a month later showed a tumor in the nasopharynx which on biopsy turned out to be nasopharyngeal carcinoma. After chemotherapy, his headaches ceased.

**Miscellaneous**

Russo et al.\(^{[35]}\) described a case of a 62-year-old man with 12 months of constant moderate pain, strictly localized in the left orbital and temporal regions with throbbing exacerbations and with ipsilateral conjunctival injection, tearing, and mild ptosis. His examination and plain MRI brain were normal. ESR was raised. He was treated as a case of GCA, but he did not improve with steroids. His subsequent contrast MRI revealed hypertrophic pachymeningitis. All secondary causes of hypertrophic pachymeningitis were ruled out. He responded to oral methylprednisolone and azathioprine.

Mainardi et al.\(^{[36]}\) described a case of 66-year-old man, with a history of migraine who developed a new headache for 4 months. It was dull, mild frontoparietal headache with several severe exacerbations daily, lasting 45–60 min, accompanied by ipsilateral lacrimation, ptosis, and nose stuffiness; onset of headaches had temporal relationship with transdermal nitroglycerine patch (TNP), recommended for coronary heart disease (unstable angina). With temporary withdrawal of TNP, the headache disappeared within a day. The reintroduction of TNP after 10 days brought the reappearance of the headache within hours; replacement of TNP by ranolazine resulted in permanent resolution of headaches.

Gantenbein et al.\(^{[37]}\) reported a series of three patients who developed a continuous hemicranial headache after cranial surgery. The first was a 44-year-old male who 3 months after excision of a left-sided vestibular schwannoma started had continuous pain without any cranial autonomic symptoms. He responded completely to indomethacin. The second patient was a 26-year-old man was treated for refractory temporal lobe epilepsy with a left-sided selective amygdalohippocampectomy with extirpation of temporomesial dysplasia. He had a skull bone infection with osteomyelitis, continuous headache radiating to the left temporal and parietal area, with superimposed stabbing attacks, with a frequency of 5–10 times/day, with duration of 30 s, and they could be triggered by forced looking to the left and could be stopped by intense squinting of the left eye. There was increased lacrimation during the attacks. Computed tomography angiography and MRI/MRA of the head revealed occlusion of the left ICA, with intramural hematoma indicating dissection. The headache was relieved by intravenous methylprednisolone, with the occasional addition of acetaminophen.
which had to be revised with two more operations. A few days after last intervention, he developed an ongoing left-sided headache with moderate-to-severe pain with ptosis and lacrimation of the left eye during pain exacerbations. He responded completely to indomethacin. The third patient was a 51-year-old female who 4 months after resection of right-sided vestibular schwannoma developed a continuous right-sided headache of moderate intensity. With exacerbations of the pain, she reported ipsilateral lacrimation and facial hot flushes. She was pain-free on indomethacin.

Alim-Marvasti et al.\cite{38} described a 40-year-old right-handed woman who woke up with a severe left-sided persistent sharp headache associated with unilateral lacrimation. The pain was mainly orbitofrontal. A few days later, her left eye appeared red. The unilateral left-sided headache was unremitting for 2 weeks with superimposed exacerbations. Then the pain, lacrimation and red-eye switched to the right side for a further 2 weeks before reverting to the left eye. Her optic disc showed drusens. All her investigations were normal, except the presence of oligoclonal bands in the cerebrospinal fluid. B-scan ultrasound scan confirmed a diagnosis of seleritis (left > right). Although not mentioned in the treatment part, authors mention in the discussion that the patient had some response to indomethacin (not absolute). She responded to corticosteroids.

A Word About Nomenclature

There is confusion regarding nomenclature for TACs which are due to some underlying cause. Some authors have used the term “secondary,” whereas others have used the term “symptomatic.” The word symptomatic is probably undesirable because it connotes a definitive relationship with a structural pathology which may not be the case and the symptoms of TACs are not specific to any etiology. Further, ICHD only recognizes the term “secondary headache.” However, the word secondary is also not without confusion as some primary TACs may evolve from episodic to chronic forms and some authors have used “secondary” (versus de novo) to underline such transitions. For example, CH may evolve from ECH to CCH and some authors have used the term secondary CCH to distinguish this group from primary CCH which were chronic from the beginning.\cite{39} Similarly, the words such as TACs-like (or cluster-like) have been used with varied interpretations and definitions. It is hoped that ICHD Committee will sort this out in the future and advocate a standardized nomenclature.

Conclusion

Nearly half of secondary TAC patients fulfill ICHD criteria for primary TAC headaches. Hence, many experts advocate routine neuroimaging in all TAC patients. Contrarily, patients of TACs with atypical features and red flags are more likely to have a secondary pathology and hence must be investigated. While reporting a case of secondary TACs, the authors should clearly mention whether the ICHD criteria are met or not, whether there are any atypical features, and whether the case is just TACs-like (mimicker). Categorization into probable, possible, and unknown based on the type of secondary cause and its treatment response along with duration of follow-up will add further clarity. Population-based studies on secondary headaches are very difficult if not impossible to conduct. Hence, real magnitude of the secondary TACs will be difficult to assess.

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Conflicts of interest

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References

1. Goadsby PJ, Lipton RB. A review of paroxysmal hemiconians, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. Brain 1997;120 (Pt 1):193-209.
2. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd ed. (beta version). Cephalalgia 2013;33:629-808.
3. Favier I, van Vliet JA, Roos KL, Witteveen RJW, Verschuuren JGJM, Ferrari MD, et al. Trigeminal autonomic cephalgias because of structural lesions: A review of 31 cases. Arch Neurol 2007; 64:25-31.
4. Favier I, Haan J, Ferrari MD. Cluster headache: To scan or not to scan. Curr Pain Headache Rep 2008;12:128-31.
5. Cittadini E, Matharu MS. Symptomatic trigeminal autonomic cephalalgias. Neurologist 2009;15:305-12.
6. Wilbrink LA, Ferrari MD, Knuit MC, Haan J. Neuroimaging in trigeminal autonomic cephalalgias: When, how, and of what? Curr Opin Neurol 2009;22:247-53.
7. Edwardsson B. Symptomatic cluster headache: A review of 63 cases. Springerplus 2014;3:64.
8. de Coo IF, Wilbrink LA, Haan J. Symptomatic trigeminal autonomic cephalalgias. Curr Pain Headache Rep 2015;19:39.
9. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: A systematic review. Cancer 2004;101:613-9.
10. Mainardi F, Trucco M, Mappioni F, Palestini C, Dainese F, Zanchin G, et al. Cluster-like headache. A comprehensive reappraisal. Cephalalgia 2010;30:399-412.
11. Favoni V, Grimaldi D, Pierangeli G, Cortelli P, Cevoli S. SUNCT/SUNA and neurovascular compression: New cases and critical literature review. Cephalalgia 2013;33:1337-48.
12. De Pue A, Larini B, Paemeleire K. Chronic cluster headache and the pituitary gland. J Headache Pain 2016;17:23.
13. Robin AM, Pabaneh AH, Mitsias PD, Schwab JM. Further evidence for a pain pathway involving the cingulate gyrus: A case of chronic cluster headache cured by glioblastoma. Stereotact Funct Neurosurg 2015;93:194-8.
14. Escutia N. Headache in a patient with an extracranial lipoma: Report of a new case. J Neurol Disord 2015;5:3-4.
15. Eswardass VP, Gnanashanmugham G, Pranesh MB, Parimalam N. A rare cause of symptomatic cluster headache. Med J DY Patil Univ 2015;8:810-2.
16. Bellamio M, Angliani M, Mainardi F, Zanchin G, Mappioni F. Cluster headache: When to worry? Two case reports. Cephalalgia 2017;37:491-5.
17. de Coo I, van Dijk JM, Metzemaekers JD, Haan J. A case report about cluster-tic syndrome due to venous compression of the trigeminal nerve. Headache 2017;57:654-7.
18. Semnic R, Kozić D, Semnic M, Trifunović J, Simić S, Radojičić A, et al. Segmental cavernous carotid ectasia in a patient with cluster-like headache. Neurol Neurochir Pol 2015;49:70-3.
19. Kao YH, Hsu YC. Chiari malformation type I presenting as cluster-like headache. Acta Neurol Taiwan 2015;24:122-4.
20. Pelikan JB, McCombe JA, Koteljuk T, Becker WJ. Cluster headache as the index event in MS: A Case report. Headache 2016;56:392-6.

21. Ljubisavljevic S, Prazic A, Lazarevic M, Stojanov D, Savic D, Vojinovic S, et al. The rare painful phenomena-chronic paroxysmal hemicrania-tic syndrome as a clinically isolated syndrome of the central nervous system. Pain Physician 2017;20:E315-E322.

22. Choi HA, Lee MJ, Chung CS. Chronic paroxysmal headache secondary to an orbital metastatic leiomyosarcoma: A case report. Cephalalgia. 2018;38:389-392. Doi: 10.1177/0333102416687538. [Epub 2017 Jan 6].

23. Taga A, Russo M, Genovese A, Manzoni GC, Torelli P. Paroxysmal hemicrania-like headache secondary to phosphodiesterase inhibitors administration: A case report. Headache 2017;57:663-4.

24. Lambru G, Trimболи M, Tan SV, Al-Kaisy A. Medullary infarction causing coexistent SUNCT and trigeminal neuralgia. Cephalalgia 2017;37:486-90.

25. Jin D, Lian YJ, Zhang HF. Secondary SUNCT syndrome caused by dorsolateral medullary infarction. J Headache Pain 2016;17:12.

26. Liapounova NA, VanderPluym JH, Bhargava R, Kolski HH. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing-like attacks secondary to head and neck trauma: Literature review and case report. J Oral Facial Pain Headache 2016;30:68-72.

27. Mangaraj S, Mishra PK, Chowdhury AK, Mohanty BK, Baliaarsiha AK. Prolactinoma presenting as short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing syndrome. J Neurosci Rural Pract 2017;8:S158-S161.

28. Brilla R, Pawlowski M, Evers S. Hemicrania continua in carotid artery dissection-Symptomatic cases or linked pathophysiology? Cephalalgia. 2018;38:402-5. Doi: 10.1177/0333102416686346. [Epub 2017 Jan 5].

29. Zhang Y, Wang D, He Z, Wu Q, Zhou J. Hemicrania continua-like headache secondary to nasopharyngeal carcinoma: A case report. Cephalalgia. 2017;37:1005-7. Doi: 10.1177/0333102416654884. [Epub 2016 Jun 10].

30. Russo A, Silvestro M, Cirillo M, Tessitore A, Tedeschi G. Idiopathic hypertrophic pachymeningitis mimicking hemicrania continua: An unusual clinical case. Cephalalgia. 2017;33:102417708773. Doi: 10.1177/0333102417708773. [Epub ahead of print]

31. Mainardi F, Zanchin G, Maggiolini F. Hemicrania continua-like headache related to transdermal nitroglycerine therapy. Headache 2017;57:494-6.

32. Alim-Marvasti A, Ho J, Weatherall M, Patel M, George S, Viegas S, et al. Trigeminal autonomic cephalgia caused by recurrent posterior scleritis. Pract Neurol 2016;16:455-7.

33. Torelli P, Cologno D, Cademartiri C, Manzoni GC. Primary and secondary chronic cluster headache: Two separate entities? Cephalalgia 2000;20:826-9.