Trigeminal autonomic cephalgias (TACs) are primary headache syndromes characterized by severe short-lasting headaches accompanied by paroxysmal autonomic symptoms.¹ The group includes cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT).² By far, CH is the most frequent syndrome and is characterized by attacks of intense periorbital or orbital pain accompanied by ipsilateral autonomic symptoms.³ These attacks may come clustered in periods of several weeks or months, alternating with attack-free periods of months to years (episodic CH) or without such attack-free periods (chronic CH). The pathophysiologic mechanism of TACs is largely unknown; hypothalamic and trigeminovascular mechanisms have been implicated.⁴ Although neuroimaging results are usually normal in TACs, associated structural lesions have been described,⁵-⁵² complicating the diagnostic and management process.

Trigeminal autonomic cephalgias (TACs) include cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. Associated structural lesions may be found, but a causal relationship is often difficult to establish. We sought to identify clinical predictors of underlying structural abnormalities by reviewing previously described and new TAC and TAC-like cases associated with a structural lesion. We found that even typical TACs can be caused by an underlying lesion. Clinical warning signs and symptoms are relatively rare. We recommend neuroimaging in all patients with a TAC or TAC-like syndrome.

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METHODS

We reviewed all patients with a symptomatic TAC or TAC-like syndrome seen in our clinics (Leiden University Medical Centre and Rijnland Hospital) in the past 3 years in which therapeutic intervention aimed at the lesion led to a substantial relief of headache. We also conducted a PubMed search for cases of TAC or TAC-like syndromes associated with underlying abnormalities between January 2001 and December 2005, using the following key-words: cluster headache, chronic paroxysmal hemicrania, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing, trigeminal autonomic cephalgia, cluster-tic syndrome, symptomatic, secondary, meningioma, tumor, arteriovenous malformation, multiple sclerosis, infarct, and intracranial. Only articles with a clear description of the location of the lesion and the headache were included. Articles not written in English were excluded.

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REPORT OF CASES

Case 1

For 2 years a 36-year-old man had short-lasting attacks of severe, stabbing headache in the temporal region, radiating to his neck and the back of his head. These headaches increased when lying down. Physical examination findings, including consultation by an ear, nose, and throat specialist, were uneventful. Results of a computed tomographic (CT) scan of the brain and an electroencephalogram at that time were unremarkable. Eight months before the patient was referred to our clinic, the duration and severity of the pain attacks suddenly increased. The stabbing pain was now localized behind the right eye. The attacks would last several hours and could be triggered by shaving, touching the right cheek, and chewing. A neurologist who had seen him during one of these attacks noticed a red, tearing eye on the right side. The diagnosis of cluster-tic syndrome was considered. Physical examination results were again uneventful.

The patient was treated with carbamazepine (maximum, 800 mg/d) and verapamil hydrochloride (360 mg/d), both with some initial efficacy for several weeks. He was further treated with 100% oxygen, without any effect. The patient was then referred to our hospital.

Because of the sudden increase in pain 8 months before, magnetic resonance imaging (MRI) of the brain was performed. This revealed an intrasellar tumor originating in the pituitary gland. The tumor had spread to the sphenoid sinus and cavernous sinus on the right side. A prolactinoma was diagnosed (prolactin level, 310 µg/L [13 478 pmol]). The patient was treated with cabergoline, 0.5 mg twice per week. The attacks resolved, and the use of all pain medication was stopped.

Several weeks later, the stabbing headache attacks increased again. The enhanced signals on the T1 and T2 images indicated a hemorrhage in the tumor (Figure 1A and B). The patient again became pain free with cabergoline treatment.

Case 2

A 24-year-old man had visited a neurologist at the age of 18 years with attacks of severe, stabbing pain above the right eye for 6 months. The attacks occurred 1 to 10 times per day and lasted for 5 minutes to 2 hours. During the attacks, he had a red eye, lacrimation, and a drooping eyelid on the side with the pain. The pain could be so intense that he would cry or press his hands against his eye. Between attacks he had mild pain behind the right eye. Physical examination results were uneventful. He was diagnosed as having a CH. A CT scan revealed no abnormalities. Treatment of the attacks with 120 mg of verapamil hydrochloride decreased the attack frequency. Several months later he complained of a reduction in vision in his right eye. A pupil anisocoria was found, and an ophthalmologist diagnosed Adie syndrome of the right eye.

At the age of 21 years, he had attacks of reduced consciousness, sometimes accompanied by vomiting in the morning. These attacks lasted a few seconds, occurred up to 10 times per day, and were accompanied by a red face, sweating hands, and restlessness. The patient was diagnosed as having epileptic seizures. Treatment with 2000 mg of valproate sodium was started, which reduced the frequency of the attacks. An MRI of the brain revealed a tumor in the cavernous sinus, extending to the right temporal lobe (Figure 2A). Both carotid arteries were surrounded by tumor tissue. A prolactinoma was diagnosed (prolactin level, 193 µg/L [8931 pmol]). Several weeks later he had

Figure 1. T1-weighted magnetic resonance images (MRIs). A, T1-weighted coronal MRI showing the intrasellar tumor. The enhanced signal indicates a hemorrhage in the tumor. The tumor extended to the sphenoid sinus and cavernous sinus on the right side. B, Gadolinium-enhanced T1-weighted coronal MRI. The tumor was contrast enhanced.
a generalized tonic-clonic epileptic attack. The patient was treated with cabergoline, 1 mg 3 times per week, resulting in a decrease in the size of the tumor (Figure 2B). Since then, he has had no more epileptic or headache attacks.

Case 3

Since the age of 59 years, a now 64-year-old woman had experienced attacks of severe pain localized around the right eye. The attacks occurred twice a week, had a duration of 30 minutes, and were accompanied by a tearing, red eye and rhinorrhea on the side of the pain. Physical examination findings were uneventful. Cluster headache was diagnosed. With 240 mg of verapamil hydrochloride, the attack frequency reduced to 6 attacks per month. An MRI of the brain revealed no abnormalities.

Verapamil hydrochloride was increased to 600 mg/d, and the attacks resolved. Later the patient developed a continuous right frontal headache. She also reported a swelling above the right eye, which was visible at physical examination. An x-ray film of the skull revealed no abnormalities, but a new MRI showed a tumor in the right orbit (Figure 3). Retrospectively, this tumor was also visible on the first MRI. The patient was referred to the ophthalmology department, where a cavernous hemangioma was removed. Postoperatively, verapamil therapy could be stopped without recurrence of headache attacks, but the continuous right frontal headache remained. The pain varied in intensity but without autonomic symptoms. A diagnosis of hemicrania continua was considered. The patient became pain free with indomethacin, 50 mg twice a day.

Case 4

For 7 years, a 60-year-old woman had experienced pain attacks in the right orbital and temporal region. These attacks lasted 90 minutes and had a frequency of 3 times per day. During the attacks she had an ipsilateral tearing eye, ptosis, and rhinorrhea. Several years before, she had been diagnosed as having right-sided glaucoma, which was considered to be unrelated to the pain attacks. Physical examination findings were uneventful. Results of a CT scan of the brain were normal. A diagnosis of CH was considered, and treatment with verapamil hydrochloride (400 mg/d) reduced the attack frequency. Oxygen (100%; 7 L/min for 15 minutes) was ineffective, but both 6 mg of subcutaneous sumatriptan and 20 mg of intranasal sumatriptan were effective.

One year later, a trabeculectomy was performed to treat the glaucoma. There was no effect on the pain attacks. Three years later, the severity and frequency of the attacks increased, and sumatriptan and verapamil ceased to be effective. An MRI of the brain revealed a tumor of the pituitary gland that extended to the right side (Figure 4). A prolactinoma was diagnosed (prolactin level, 157 µg/L [6826 pmol]), and she was treated with cabergoline, 0.5 mg twice a week. The headache attacks disappeared, and she has been free of pain up to now.

PubMed SEARCH

We found 54 TAC or TAC-like cases in the literature associated with a structural lesion. We excluded 3 reports of patients with...
CH after orbital exenteration9,10 and cases with first onset of the headache in association with abnormalities at neurologic examination that clearly pointed to an underlying cause (eg, a sudden hemiparesis associated with an ischemic infarct).7-12 We also excluded 16 cases without therapeutic intervention for the lesion or without description of the headache after intervention, since a causal relationship between the lesion and the TAC would have been difficult to establish13-28 (Figure 5). Two cases with an arteriovenous malformation were also excluded from our series because causality could not be assumed. In one patient, partial embolization had no effect,29 and in another patient, there was a shift of the headache side after embolization.30

RESULTS

In the remaining 27 cases from the literature12,26,27,31-52 (including 2 of our own51,52) and the 4 new cases, there was a significant improvement or even disappearance of the headache after therapeutic intervention aimed at the structural lesion (eg, surgery, embolization, radiotherapy, or medical therapy) (Table). Sixteen of the 31 patients had a clinical picture fully compatible with the International Headache Society criteria for CH or PH. One patient had a typical cluster-tic syndrome. Four patients were diagnosed as having a typical SUNCT. One of them was first diagnosed as having trigeminal neuralgia with lacrimation and redness of the right eye53 because the term SUNCT was coined only a year later.53 The remaining 10 patients had an atypical TAC: 9 with 1 atypical feature and 1 patient (case 2) with 2 atypical features. Atypical features included abnormal attack duration (n=4), abnormal attack frequency (n=2), a continuous headache (n=1), absence of autonomic symptoms (n=2), and bilateral autonomic symptoms (n=2). Four patients (2 with a typical TAC) developed a background or continuous headache during the disease.

In 27 patients, the lesion was ipsilateral to the attacks. Two patients had a bilateral lesion (and unilateral attacks), and 1 patient had bilateral attacks (and a unilateral lesion). In 1 patient, a (unilateral) lesion contralateral to the attacks was reported.30 In 10 cases, vascular abnormalities (including arteriovenous malformations, aneurysms, and artery dissections) presumably caused the symptoms. Tumors were found in 18 patients, of whom 11 had pituitary tumors. The remaining 3 patients had various diseases (eg, infectious, foreign object, or mucocele).

Individual cases showed subtle signs, such as testicular atrophy, fever, and the absence of the radial pulse on one side at onset of the headache. A sudden increase in attack frequency or intensity or development of physical abnormalities (ophthalmoplegia, permanent ptosis, swelling above the eye, acromegaly, amenorrhea-galactorrhea syndrome, Adie syndrome, sudden loss of consciousness, hyperreflexia, or Babinski sign) was described in 13 patients, 2 of whom developed abnormalities and had a worsening of the headache.

In 10 patients, the headaches were reported to be drug resistant; in 1 patient no response to drug therapy was described. In the other patients a variety of drugs were reported to be effective (eg, simple analgesics, verapamil, lithium, indomethacin, and corticosteroids).

Sixteen patients had a chronic pattern of the TAC: 9 had a diagnosis of CH, 3 had PH, 3 had SUNCT, and 1 had cluster-tic syndrome. Seven patients had an episodic pattern of the TAC, and all were diagnosed as having CH. In another 7 patients, the TAC was diagnosed shortly before the study, so it cannot be determined whether these cases were episodic or chronic TAC because the follow-up was too short. In one case, no description of the pattern was given.
We aimed to identify clinical clues to indicate when to consider neuroimaging in patients with a TAC. We reviewed 27 published and 4 previously unpublished new cases in which a TAC or TAC-like syndrome was associated with a structural lesion and treatment of the lesion had resulted in a significant clinical improvement. Only 10 patients had atypical symptoms, including abnormal attack duration, absence of autonomic symptoms, bilateral autonomic symptoms, or a continuous headache. A sudden increase or change in symptoms or development of abnormalities at physical examination during follow-up was reported in 13 cases and would obviously be a reason to search for underlying abnormalities.
The most remarkable finding was that important causal lesions, such as large cerebral tumors, could be found even in patients with a typical TAC, fulfilling all International Headache Society criteria, with a typical episodic time pattern and responding to TAC treatment. Because of the important implications, this suggests that neuroimaging should always be considered in patients with a TAC, although the likelihood of finding clinically relevant lesions will probably be low.

In a remarkably high number of patients (n=11), a pituitary tumor was found. A recent study also showed that headache is a common symptom of pituitary disease: 84 patients with troublesome headache and a pituitary tumor were evaluated; 7 of them were diagnosed as having a TAC, although no clarity was given about the causality between the tumor and the headache in the individual patients. In our review, only 1 patient had a nonfunctioning adenoma, suggesting that tumor activity may be important. In conclusion, even typical TACs can be caused by an underlying lesion. We recommend neuroimaging in all patients with TACs.

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