TUTORIAL

Andrea Romano
Valentina Cipriani
Alessandro Bozzao

Neuroradiology and headaches

A. Romano (✉) • V. Cipriani • A. Bozzao
Department of Neuroradiology,
La Sapienza University of Rome
Sant'Andrea Hospital
Via di Grottarossa 1035
I-00189 Rome, Italy
E-mail: andrea.romano@uniroma1.it

Abstract Headache is one of the most common outpatient pain conditions encountered in both physician offices and emergency departments. Establishment of an accurate diagnosis, accomplished only by a thorough history followed by a physical examination, is critical before treatment can be initiated. Many patients undergo evaluation with computed tomography and more recently magnetic resonance imaging to exclude important abnormalities. It is known that a little percentage of patients showed significant neuroradiologiacal abnormalities and the rate of significant intracranial abnormalities in patients with headache and normal neurological examination exists.

Keywords Headache • Magnetic resonance • Computed tomography

Introduction

Headaches with attendant pain and debilitation have been noted throughout recorded medical history. New great scientific results have been obtained since the aetiologic theories included curses of the gods, evil spirits, imbalance of humours and many other equally imaginative ideas. Today, fortunately, some things have changed [1].

Headache is one of the most common outpatient pain conditions encountered in both physicians' offices and emergency departments. Establishment of an accurate diagnosis, accomplished only by a thorough history followed by a physical examination, is critical before treatment can be initiated.

Although the majority of patients who present with chronic or recurrent headache do not have neurological abnormalities, many patients undergo evaluation with computed tomography (CT) and more recently magnetic resonance imaging (MRI) to exclude eventual diseases responsible for the symptoms. MRI is more sensitive than CT in the detection of almost all intracranial abnormalities. Despite this, limited data exist about the utility of head MRI in patients with headache. In a recent paper from Sempere et al. [2], which considered 1876 patients with headache (any type started 4 weeks before neuroimaging), 1.2% of patients showed significant neuroradiological abnormalities and the rate of significant intracranial abnormalities in patients with headache and normal neurological examination was 0.9%. The authors

concluded that the proportion of patients with headache and intracranial lesions is relatively small, but neither neurological examination nor the features in the clinical history permit us to rule out such abnormalities. There is general agreement that imaging should be performed in case of important changes in the type of headache, in case of first or worst episode, when the onset is sudden or provokes awakening during sleeping, when neurological symptoms are associated, in very young or old people (over 5 and 50 years), in patients with cancer and pregnancy, when there are consciousness changes and when headache is related to Valsalva manoeuvres or sexual activity.

In the first part we will discuss the main neuroradiological findings that can be evaluated in primary and secondary headaches by conventional imaging. In the second part of this tutorial we will report the more recent results in the applications of "functional" imaging in the study of pathophysiology of primary headache.

"Conventional imaging" in primary headaches

Migraine

Migraine is thought to be a progressive inflammatory neurovascular disorder associated with considerable disability and impairment of quality of life. It is a disease accompanied not only by characteristic throbbing pain, but also by associated symptoms and disability. Migraine headache frequently is preceded by a prodrome, known as aura. The aura in migraine is a clearly defined neurologic deficit, most often visual in nature, such as scotomas or visual field changes [1].

The role of imaging and specifically of conventional MRI is still debated. The association of migraine phenomena with neuroimaging abnormalities, as demonstrated by CT and MRI, has been the subject of much debate [3].

In a study by Ziegler et al. [4], 18 cases of migraine with aura were considered. Only in four of the migraine patients were areas of increased signal intensity in T2-weighted images identified. In three of the normal controls similar areas were seen as well. The authors concluded that these small areas, difficult to identify, may be of multiple aetiologies. Similar small unidentified bright areas have been seen not uncommonly in the asymptomatic older population.

In another study, by Igarashi et al. [5], the authors assumed that repetition of migraine, with repeated episodes of cerebral hypoperfusion responsible for aura, could cause permanent ischaemic changes in the brain. The characteristics of MRI lesions in migraine were well defined small foci on T2-weighted and proton density-weighted images in the white matter. These white matter lesions resemble so-called unidentified bright objects (UBOs) [6], which are often related to ageing, hypertension and other atherosclerotic risk factors. In this study 39.6% of patients with migraine showed small white matter lesions on MRI. The incidence of white matter lesions was not different between patients with and without aura. No significant links with risk factors were found. A group of patients with migraine under 40 years old without risk factors showed significantly higher incidence of positive MRI changes (29.4%) than the controls (11.2%). The side of the MRI lesions did not always correspond to the side of usual aura or headache. The migraine may be associated with early pathologic changes in the brain. MRI studies in patients with migraine showed focal areas of high intensity on both T2-weighted and proton density-weighted MR images distributed bilaterally in the white matter of the brain [5].

These results are similar to those report by Soges et al. [7], who studied 24 patients with migraine and found 46% of them showed abnormal MRI studies. Their slightly higher percentage for positive MRI might be explained by the slightly older mean age (36.8 years) than Igarashi et al.'s patients (34.0 years).

The most tempting speculation to explain brain lesions in migraine is that repeated attacks of hypoperfusion during aura might cause permanent ischaemic changes [5] and frequency of attacks is an important indicator of existence of white matter foci [8].

Ischaemia or an immune-based white matter demyelinisation are other possible mechanisms for the white matter lesions [9].

Such high incidence of hyperintense foci in the white matter of patients with migraine was not confirmed by other studies. Osborn et al. demonstrated parenchymal brain lesions in only 12% of patients with migraine with aura [10].

In a recent study published in *JAMA* in 2004, no significant differences between patients with migraine and controls in overall infarct prevalence were found. However, in the cerebellar region, patients with migraine had a higher prevalence of infarct than controls. Among women, the risk for higher white matter lesion load was increased in patients with migraine compared with controls. This risk increased with attack frequency [11].

The same authors more recently underlined that brain infarction occurs far more frequently than expected in migraine patients, being most pronounced in migraine with aura (8% have subclinical cerebellar infarcts). Most infarcts remain clinically silent. Female migraine patients are at increased risk of deep white matter lesions, independent of the effects of cardiovascular risk factors. The

influence of migraine severity (attack frequency) on the risk of both types of lesions suggests a causal relationship between migraine severity and lesion load [12].

In a recent meta-analysis from Swartz and Kern, the authors demonstrate that subjects with migraine are at higher risk of having white matter abnormalities on MRI than those without migraine. This increased risk is present even in younger individuals who do not have co-occurring cerebrovascular disease risk factors [13].

Tension-type headache

Benedittis et al. showed that in the MRI of patients with tension-type headache there is a higher incidence of white matter abnormalities compared to control subjects (33.3% *vs*. 7.4%). These lesions are distributed predominantly in the frontal region and were shown to have a similar incidence compared with patients with migraine with aura (32.1%) [14].

Cluster headache (CH)

No specific abnormalities have been described in cluster headache in conventional MRI. When an acute CH attack was triggered with nitroglycerin (NTG), vasodilatation was observed with PET occurring in the ipsilateral posterior inferior hypothalamic grey matter, in the contralateral ventroposterior thalamus, in the anterior cingulate cortex, in the ipsilateral basal ganglia, in the right anterior frontal lobe and in both insulae. In patients out of the group who experienced only a mild NTG headache, activation was seen bilaterally in the insulae and frontal cortices, the anterior cingulated cortex, the right thalamus and the left basal ganglia, but not in the hypothalamic grey area. In addition, the authors found significant activation (vasodilatation) in the region of the major basal arteries, which was caused in part by NTG but was also observed in the spontaneous case and could be induced by capsaicin injection into the forehead [15].

"Conventional imaging" in secondary headaches

Headaches are one of the most common symptoms that neurologists evaluate. Although most are caused by primary disorders, the list of differential diagnoses is one of the longest in all of medicine, with over 300 different types and causes [16].
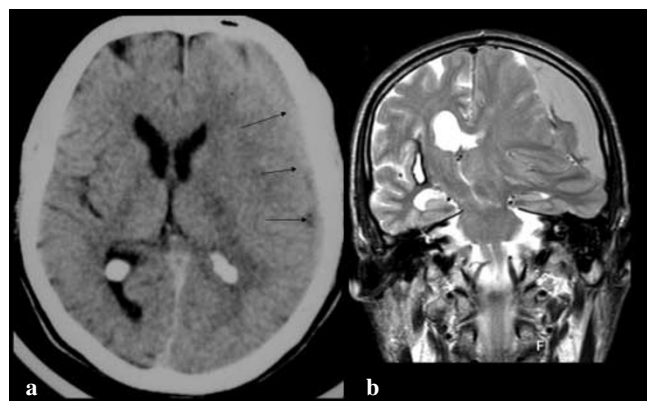
Fig. 1 Subdural haematoma on CT (**a**) and MRI (**b**) images. In these cases CT and, even better, MRI can show the haematoma and the brain compression

### Headache attributed to head and/or neck trauma

The main pathologies responsible for this type of headache are represented by traumatic intracranial haematoma, epidural or subdural haematoma and also by post-traumatic acute or chronic head injury. Craniotomy might be responsible for this form of headache as well. Subdural haematoma (Fig. 1) must be considered, especially in elderly people, because the traumatic event can be unremarkable and no specific neurological symptoms might be associated. In these cases CT and, even better, MRI can show the haematoma and the eventual brain compression leading to possible surgical procedures [17].

### Headache attributed to cranial or cervical vascular disorders

The pathologies responsible for this type of headache are transient ischaemic attacks (TIA), ischaemic stroke, intracranial or subarachnoid haemorrhage (SAH), saccular aneurysm, arterio-venous malformation (AVM), arteritis (Gigant cell arteritis), carotid artery dissection, cerebral venous thrombosis and pituitary haemorrhage.

SAH (Fig. 2) must be considered when a new episode of headache is present associated to nuchal rigidity. In the acute phase of SAH, CT is the study of choice, being able to show even a small amount of blood in the subarachnoid spaces. If SAH is demonstrated by CT scan, spiral CT angiography can identify the presence of the aneurysm responsible for SAH, thus indicating a need for further treatment (surgical or endovascular). If the clinical episode is far from the radiological evaluation, MRI might be more sensitive in detecting subarachnoid blood when FLAIR sequences are used. These sequences typically show the blood with high signal intensity compared to the normal cerebrospinal fluid.

Unruptured vascular malformations can be responsible for prolonged headache. Artero-venous and dural malformations cause changes in brain vascular haemodynamics. MRA and CTA can easily show unruptured vascular malformations but conventional angiography is still mandatory to understand the exact structure of the abnormality. Also the presence of arteriovenous (AV) shunts, such as patent foramen ovale (PFO), can represent a trigger for migraine with aura attacks. A higher prevalence of PFO was demonstrated in migraineurs vs. the normal population [18].
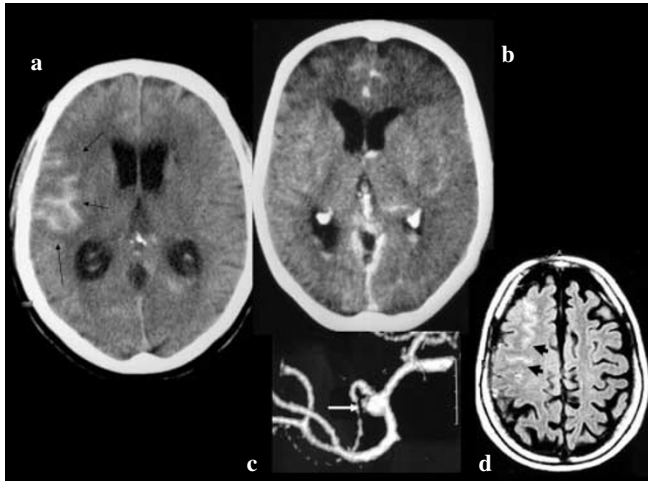
Fig. 2 Subarachnoid haemorrhage (SAH). In (**a**) and (**b**) a SAH in the acute phase is evident on the CT study. CT angiography study (**c**) demonstrates the presence of the aneurysm responsible for SAH in the M2 segment of middle cerebral artery (*arrow*). FLAIR sequence might be more sensitive than CT in detecting subarachnoid blood in the first days after the acute event. The blood is shown as a high signal intensity alteration compared to the normal cerebrospinal fluid (**d**, *arrow*)
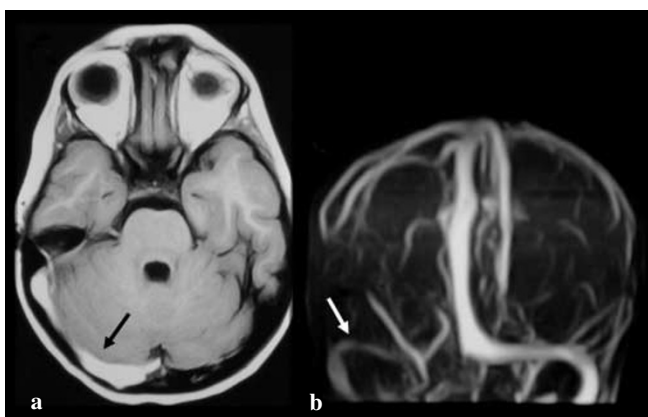

Fig. 3 Right transverse and sigmoid sinuses thrombosis. The T1 hyperintensity inside the sinuses (**a**) and the occlusion of them in the MR angiography study are evident (**b**). The high signal in MIP reconstruction of MRA is due to the intrinsic hyperintensity of the clot visible on conventional axial T1-weighted images (*arrows*)

Venous thrombosis (Fig. 3) should be considered when dealing with young women using hormone therapy [19]. Venous thrombosis can be identified by means of MRI and MRA or by CT angiography. Parenchymal lesions (frequently haemorrhagic) can be associated as well.

Carotidynia is a syndrome encompassing many varieties of pain in the carotid region. It can be due to carotid dissection (Fig. 4). In case of suspect carotid dissection, a high signal on T1W can be demonstrated in the wall of distal internal carotid artery. The haematoma might produce a reduction of the lumen size at MRA. Neurological symptoms (either central deficit or hypoglossal nerve compression) can be associated [17]. Migraine may represent a predisposing condition for spontaneous cervical artery dissection [20].

Pituitary haemorrhage can cause a sudden and strong headache. This may be related to previous therapy for pituitary adenoma or not. MRI can easily show the blood inside the gland and follow-up can document partial or complete resolution of the disease (Fig. 5). Close follow-up must be considered to rule out a dangerous optic nerve compression.
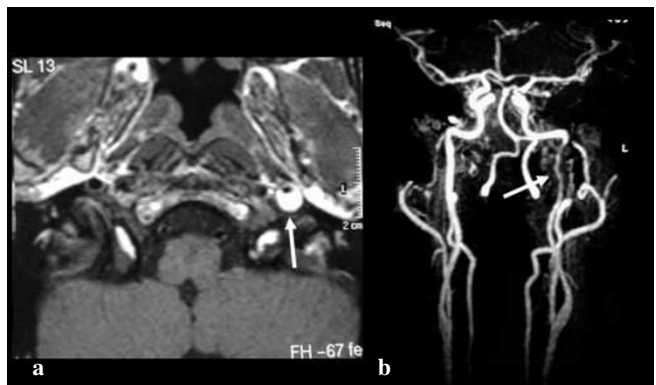
Fig. 4 Carotid dissection. High signal on T1-weighted image is observed in the wall of left distal internal carotid artery (**a**, *arrow*). The haematoma produces a reduction of the lumen size at MRA (**b**, *arrow*)
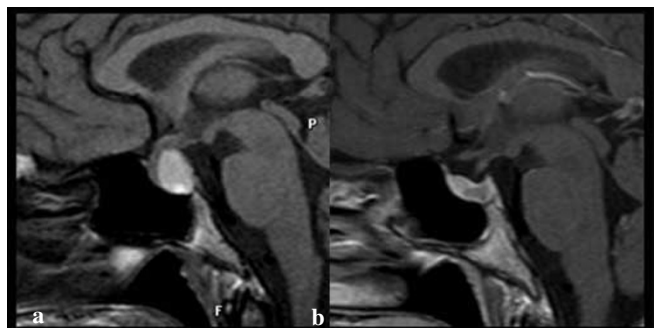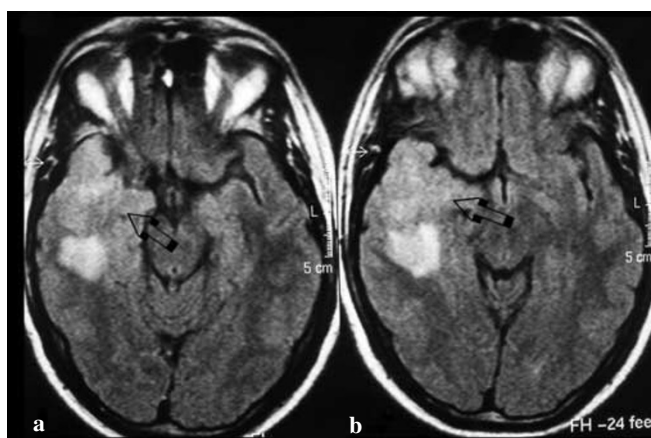

Fig. 5 Pituitary haemorrhage observed as a hyperintense area inside the gland in the acute phase (**a**) and as an area of reduced vascularisation post-contrast (**b**) in the follow-up

Headache attributed to non-vascular intracranial disorder

There are many non-vascular intracranial disorders responsible for headache-like idiopathic intracranial hypertension, high or low cerebrospinal fluid pressure, aseptic meningitis, intracranial neoplasm, epilepsy, hypothalamic or pituitary hyper- or hyposecretion.

Only a minority of patients who have headaches have brain tumours. Some locations are more likely to produce headache (e.g., a posterior fossa tumour causes headache more often than a supratentorial tumour) [21].

All slow-growing intracranial neoplasm, typically low-grade gliomas, but also benign arachnoid cysts, may lead to headache without specific neurologic symptoms (Figs. 6, 7). All the pathologies able to cause changes in

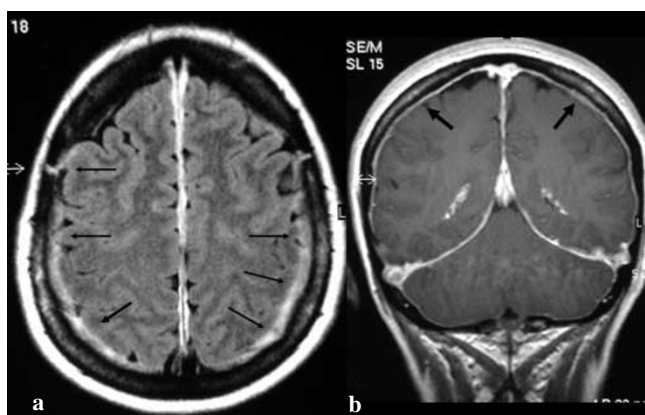the cerebrospinal fluid circulation leading to hydrocephalus should be considered as well (Fig. 7).

In a study by Boiardi et al. [22], the author showed that a headache hiding a brain tumour is rather similar to a tension headache in 77% of cases. In 5%–10% of cases it could mimic a classic migraine; otherwise it presents as a mixed form with tension and classic migraine combination. Some studies investigated the indications of neuroimaging studies in the evaluation of different types of primary headaches [23]. In particular, in a study by Wang et al. [24], more than 400 patients with chronic headache were retrospectively reviewed. From these results it emerged that the atypical headache type was the most significant predictor of organic causes.

The typical findings of idiopathic intracranial hypertension (pseudotumour cerebri) are represented by small ventricles, poor visualisation of subarachnoid spaces and dilatation of the perioptic nerve sheaths. Chronic sinus thrombosis must be excluded using MRA with gadolinium-enhanced techniques. Other possible causes like Chiari I malformations (Fig. 7) must be considered and identified looking at the position of cerebellar tonsils on the midline sagittal MRI.

In case of low CSF pressure (Fig. 8), small subdural fluid collection has been described showing enhancement after intravenous injection of gadolinium. These findings can be appreciated behind the clivus as well. Idiopathic form should be differentiated secondary form, looking for cerebrospinal fluid leakage in the spinal roots. This is actually done, in the first step, using a myelo-MR examination.

Fig. 6 Low-grade glioma of the right temporal lobe as seen in these T2-weighted MRI (FLAIR sequences) (**a**, **b**, *arrows*)

Headache attributed to infection

Bacterial or lymphocytic meningitis, encephalitis, brain abscess, subdural empyema and systemic infection may

Fig. 7 Possible causes of derangement of cerebrospinal fluid circulation. Chiari I malformations (**a**), arachnoid cyst (**b**) and colloid cyst (**c**). In **a** and **c** ventricular dilatation is the cause of endocranic hypertension. In **b** the growth of the arachnoid cyst can lead to brain compression

Fig. 8 A case of low CSF pressure with bilateral small subdural fluid collection (**a**, *arrows*) and dural enhancement after intravenous injection of gadolinium (**b**)

be responsible for headache. This type of headache is characterised by diffuse or continuous pain accompanied by nausea and/or focal neurological symptoms and/or signs. A direct space-occupying effect leading to raised intracranial pressure and/or irritation of the meningeal or arterial structures are the mechanisms for causing headache [17].

MRI with diffusion-weighted images (DWI) can be easily characterised by the presence of a brain abscess due to the typical restriction of diffusion inside the abscess cavity. Using these imaging characteristics we can easily differentiate an abscess from the presence of necrosis inside a primary (glioblastoma) or a secondary (metastasis) tumour of the brain.

Headache attributed to disorders of homeostasis

A lot of disorders of homeostasis cause headache, such as hypoxia, hypercapnia, arterial hypertension, hypothyroidism, hypertensive encephalopathy, pre-eclampsia and eclampsia, anaemia, adrenocortical insufficiency, hyperaldosteronism, polycythemia, Cushing's disease etc. [17].

In eclampsia MRI can demonstrate typical reversible signal alterations in the parieto-occipital regions.

Headache or facial pain attributed to disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures

Pain in the oro-facial region can be very distressing for the patient, as it usually affects important daily living functions, such as chewing, swallowing, talking and laughing. Temporo-mandibular disorders constitute the second most common cause of oro-facial pain, following dental pain.

Clinical examination of the oro-facial pain patient includes assessment of cranial nerve function, cervical spine evaluation, palpation of masticatory and neck muscles, temporo-mandibular joint examination and complete intra-oral and dental evaluation.

Cervicogenic headache
In 16% of cases the lateral atlanto-axial joint is responsible for headaches. Tumour of the same region may lead to cervicogenic pain as well (Fig. 9). There is no clinical correlation between changes seen MRI and common 'abnormalities' such as disc degeneration, disc bulges, arthritis and potential sources of patient's pain [25].

Trigeminal neuralgia
In idiopathic form the typical clinical pattern is associated with a normal neurological and MRI examination. The most common cause of this form is a compression of trigeminal nerve root by an aberrant loop of blood vessels (Fig. 10). In a study by Robert et al. [26], MRI demonstrated that a compression of the fifth cranial nerve at the root entry zone [27–29] by a vascular structure can be responsible for trigeminal neuralgia. In another study by Charles et al. [30], a vascular conflict with trigeminal nerve at the root entry zone was seen on FISP images (a type of thin high-resolution imaging with high signal inside the vessels) in 10 of 13 (77%) symptomatic nerves and only in 8 of 113 (7%) asymptomatic nerves. MP-RAGE and FISP images demonstrated arterial contact equally well. The superior cerebellar artery is by far the most common vessel causing trigeminal compression (80% of cases). In case of nerve conflict the artery typi-
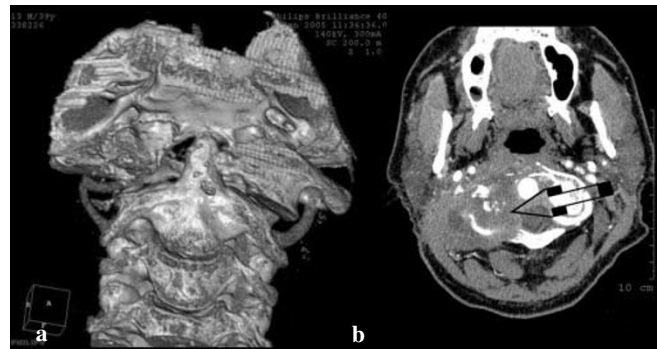
Fig. 9. Sarcoma of C2 in a patient with persistent pain in at the base of the skull. (**a**) 3D reconstruction and (**b**) axial CT scan (*arrow*)
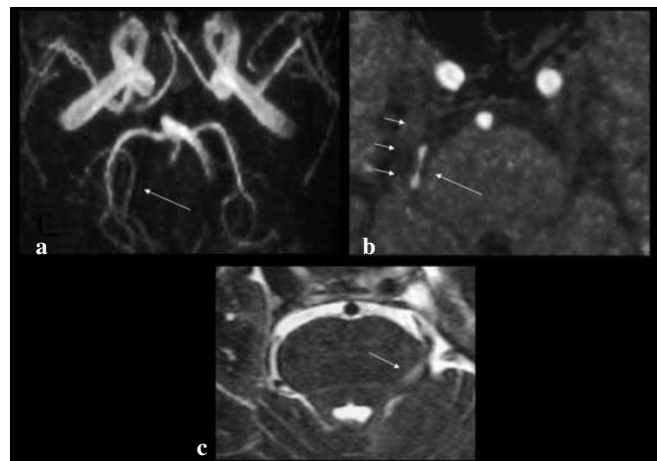
Fig. 10 Neurovascular conflict. An aberrant loop of superior cerebellar artery is the most common vessel causing trigeminal compression on its root entry zone (**a**, **b**, *arrows*). It is possible to see a hyperintensity on T2-weighted images in the intrapontine segment of the trigeminal nerve (**c**, *arrow*)

cally runs medially to the main trigeminal root. A T2 signal alteration can be eventually present in the intra-pontine segment of the nerve (Fig. 10). In 15% of patients with trigeminal neuralgia the cause of the disorder is represented by multiple sclerosis (Fig. 11) (especially in young patients and when pain is bilateral), with a prevalence of 2%. Rarely, other structural lesions, mainly localised in the pontine region, can lead to trigeminal neuralgia. These include vestibular or rarely trigeminal schwannoma, meningiomas, epidermoid or other cysts (Fig. 12). Vascular brainstem lesions, especially pontine infarctions, angiomas or artero-venous malformations, are further causes of symptomatic trigeminal neuralgia [31].

Pain around the eye

This is associated with disturbed vision and can be a presenting complaint for several ocular disorders. The common neurological disorders that cause pain around the eye are optic neuritis, inflammatory or infectious diseases, temporal arteritis and skull base fractures with lesions of ocular motor nerves.

In case of optic neuritis MRI can show a T2 signal hyperintensity in the affected, often oedematous nerve,

with increased gadolinium uptake in the acute phase of the disease [31].

Temporo-mandibular disorders (TMD)

The term refers to a variety of pathologic conditions that affect the masticatory musculature, the temporo-mandibular joints or both. TMD are classified into 3 main categories: masticatory muscle disorders, articular disc derangements and temporo-mandibular joint disorders.

MRI can be used to substantiate the clinical diagnosis concerning articular disc displacement. Articular disc derangements are usually characterised by displacement of the articular disc anteriorly and medially.

Disc displacement with reduction (Fig. 13) is characterised by improvement of the position of the displaced disc during opening. An opening and closing joint clicking can be heard but pain may or may not be present. Disc displacement without reduction refers to an altered disc-condyle structural relation that is not improved during mouth opening.

Fig. 12 Epidermoid lesion (**a**) and trigeminal schwannoma (**b**, *arrow*) leading to trigeminal neuralgia

Fig. 11 Young patient affected by multiple sclerosis with trigeminal neuralgia. An active plaque close to the intrapontine segment of the trigeminal nerve is evident in this MRI FLAIR image (*arrow*)
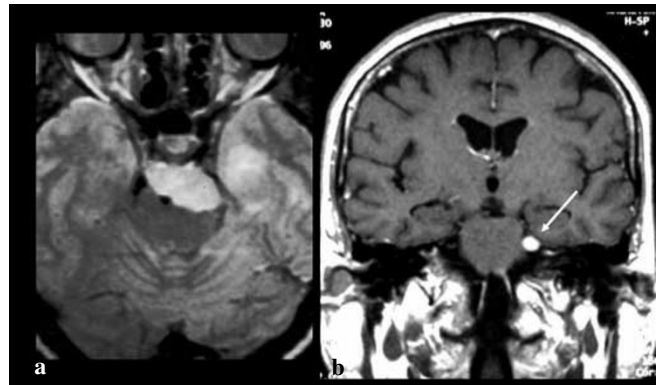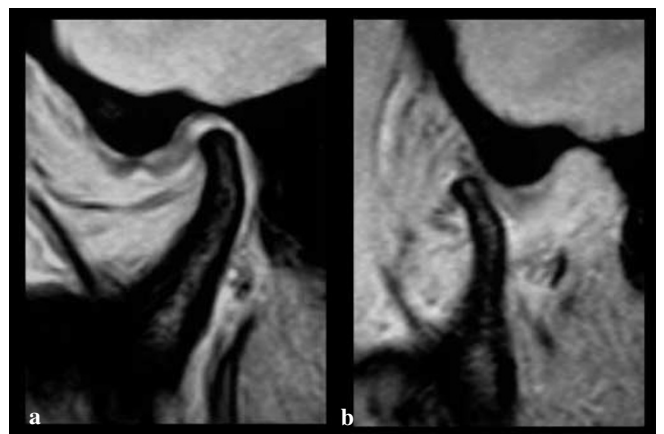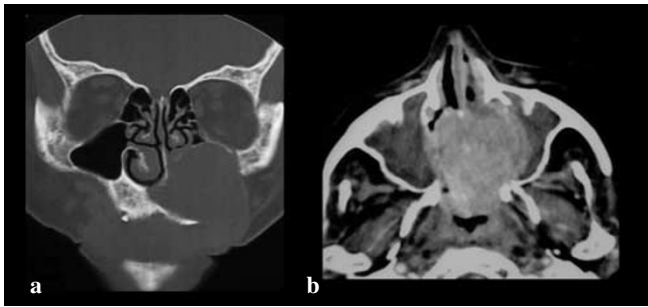
Fig. 13 Temporo-mandibular disorder. Articular disc displacement anteriorly (**a**). Reduction is characterised by improvement of the position of the displaced disc during opening (**b**). An opening and closing joint clicking can be heard but pain may or may not be present

Fig. 14 (**a**) CT scan (coronal view) of a large mucocele of the maxillary sinus; (**b**) CT scan with contrast injection (axial view) of a patient with carcinoma of the paranasal sinuses

Pain is typically present in the acute condition, while chronic disc dislocation may be non-painful [32, 33].

Rhinosinus-related headache
Sinusitis is overdiagnosed as a cause of headache because of the belief that pain over the sinuses must be related to the sinuses. In fact, frontal head pain more often is caused by migraine and tension-type headache [34].

The best diagnostic yield is obtained with CT. Axial and coronal reconstruction from volumetric data can easily show the presence of sinus disease (Fig. 14), while MRI is mandatory in patients with signs of intracranial complications. Standard radiographs are false negative in about a quarter of patients and should be avoided [31].

Idiopathic (Bell's palsy)
This is a common disorder and is often associated with facial pain localised around the ear, jaw angle and neck. Symptomatic facial palsy due to different underlying conditions, most often inflammatory, infectious, compressive, infiltrative diseases or parotid tumours or lesions in the cerebellopontine angle like acoustic neurinoma, meningioma, cystic lesions or aneurysms, tend to be associated with hypoacusia, vertigo or facial palsy [31].

Functional neuroimaging of primary headaches

Introduction

The diagnosis of the various headache disorders is based on clinical features as described by the International Headache Society criteria. Neuroimaging of headache patients has dramatically changed our understanding of the pathophysiology of primary headaches and provided a unique insight into these syndromes [35]. Functional neuroimaging of patients with headache is useful to study the pathophysiology rather than for diagnostic purposes. To understand the functional imaging possibilities in headaches, it is necessary to remember how pain structures participate in painful conditions other than headache. In migraine with aura the primary event occurs in the cortex and, including hypothalamus and thalamus, it finishes in the cortex, manifesting pain. In migraine without aura, brainstem findings suggest a dysfunctional pain system [36].

Migraine with aura
Migraine represents the classic primary headache and it is considered to have a primarily vascular pathogenesis. The pathophysiological concept of *vascular headaches*, however, is based on changes in vessel diameter or in cerebral blood flow. These mechanisms would trigger pain. Regional cerebral blood flow (rCBF) studies have emphasised a dysfunction of the cerebrovascular regulation in headache.

Changes in rCBF, shown by positron emission tomography (PET) studies, reflect variations in vessel diameter and synaptic activity (inhibition and excitation). Experimentally inducing cranial pain, activation (i.e., increase in rCBF, bilaterally) in the anterior cingulate cortex, both insulae, the contralateral thalamus and the cerebellum are evident [37].

Before these technological advances, knowledge of the pathogenesis of migraine was based largely on clinical observations. Harold G. Wolff [38] proposed that the neurological symptoms of the migraine aura were caused by cerebral vasoconstriction and the headache by vasodilatation. Lashley [39] assessed that cortical spreading depression (CSD) of Leao was the primary cause, introducing the concept of the neural theory of migraine [40].

The slow progression of the visual and sensory migraine symptoms are characteristic of the electrophysiological series of events known as CSD. CSD is a wave of electrical activity followed by neuronal depression, spreading across the cortex at approximately 3–6 mm/min [41]. Numerous studies have confirmed that the aura phase of migraine is associated with a reduction in cerebral blood flow [42]. This flow change moves across the cortex as a 'spreading oligaemia' at 2–3 mm/min [37]. Sanchez del Rio et al. reported the results of perfusion weighted images studies in a total of 28 spontaneous episodes of migraine. The authors observed decreases in rCBF and rCBV and increases in mean transit time (Fig. 15) in the visual cortex contralateral to the affected visual field during 7 episodes of visual aura and 7 episodes of headache after resolution of the aura. No significant perfusion was evident in other brain regions. Blood flow changes observed during migraine visual aura do not go over the threshold associated with ischaemic injury, justifying the absence of lesions in diffusion images [43].
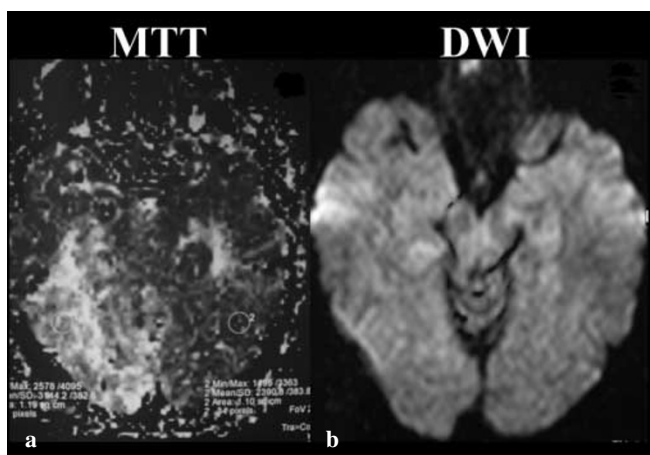
Fig. 15. Increases in MTT perfusion MRI map (**a**) in the visual cortex contralateral to the affected visual field during an episode of visual aura. Other brain regions do not show any perfusion changes during the aura or during headache. Blood flow changes observed remain above the threshold associated with ischaemic injury, justifying the absence of lesions in diffusion-weighted images (**b**)

Cerebral perfusion changes during migraine with aura have been described also by BOLD functional MRI studies. In the typical visual aura of migraine, functional MRI has revealed multiple neurovascular events in the occipital cortex, resuming the CSD: (1) an initial hyperaemia lasting 3.0–4.5 min, spreading at a rate of 3.5 mm per min, (2) followed by mild hypoperfusion lasting 1–2 h, (3) an attenuated response to visual activation and (4) like CSD, in migraine aura, the first affected area is the first to recover [43].

In a recent case report [44] reversible changes located in the right parieto-occipital cortex on DWI images were described in a patient with acute onset of headache. The presence of positive DWI images, with the absence of low apparent diffusion coefficient value, referred to vasogenic oedema, could be in accordance with focal prolonged hyperperfusion associated with vasogenic leakage. The correlation and complete resolution of both clinical and neuroimaging abnormalities could validate a reversible neuronal inflammatory pathology in migraine with typical aura. Another similar finding has been described by Jacob et al., in which the author reported the case of a young woman affected by sporadic hemiplegic migraine (SHM) with reversible changes on MRI. In this case, both DWI and ADC maps were positive for restricted diffusion of water; perfusion maps showed increased vascularity and after gadolinium, an enhancement of grey matter in the affected regions was evident. Spectroscopy study showed reduced NAA/Cr. To explain these results, in the absence of vascular occlusion, the authors suggested a metabolic alteration at cellular level with a spreading cortical depression leading to damage of the ATPase pump with altered membrane permeability [45].

In the last few years, several studies of magnetic resonance spectroscopy, a non-invasive technique that allows the investigation of variations in some cerebral metabolites, and in particular ^{31}phosphorus, demonstrated a metabolic disturbance in the brain of migraine patients with aura and, to a lesser extent, of migraine patients without aura, which is evident even in the interictal period.

Such alterations concern energy metabolism and consist of increased inorganic phosphorus and ADP, reduced phosphocreatine and decreased phosphorylation potential. A mitochondrial dysfunction was hypothesised to be the biochemical substrate that could contribute to brain cortical hyperexcitability [46].

In a recent ^{1}H-MRS study, focused on visual cortex, before and after photic stimulation, a consistent decrease in the NAA signal in migraine with aura patients compared with migraine without aura patients and control individuals was noted [47]. In migraine with visual aura patients associated with paraesthesia, paresis or dysphasia (Maplus), lactate increased only during stimulation, only in visual cortex; in migraine with aura patients, resting lactate was high in visual cortex, without further increase during stimulation [48].

In the interictal period Watanabe et al. found high lactate levels, speculating that anaerobic glycolysis occurs in patients with migraine [49].

Migraine without aura
Friberg and colleagues [41] demonstrated with SPECT that interictally almost 50% of migraine without aura sufferers had abnormal interhemispherical asymmetries in rCBF. These asymmetries were discrete compared to those seen during the aura phase of a migraine attack. In a study of the same group [50], middle cerebral artery (MCA) velocity studied by transcranial Doppler sonography on the headache side was significantly lower than that on the non-headache side. The authors concluded that in the headache phase there might be a dilatation in the MCA on the headache side [37].

Cluster headache
Using PET, a possible site of the central origin of cluster headache has been visualised in the hypothalamic grey matter [51]. During an acute attack, activation occurs in frontal areas, both insulae, contralateral thalamus and cingulate cortex. A specific activation was demonstrated in the ipsilateral hypothalamus. This region is specific for cluster headache, as it has not been seen in migraine [37].

Structural imaging with voxel-based morphometry has identified an area in the posterior hypothalamic grey as key in understanding cluster headache. This area is subtly enlarged in its grey matter volume, active during an acute cluster headache [52].

In patients with cluster headache, both N-acetil aspartate/creatine and choline/creatine levels were significantly lower in comparison with either the control or chronic migraine groups. Low levels of N-acetil aspartate/creatiner and choline/creatine suggest that cluster headache might be related to both hypothalamic neuronal and myelin dysfunction or loss in patients with cluster headache [52–54].

Brain ^{31}P-MRS showed reduced phosphocreatine levels and an increased ADP concentration, as in various types of migraine, suggesting the presence of similar pathogenic mechanisms between cluster headache and migraine [55].

Tension-type headache
Using MRI and voxel-based morphometry, structural abnormalities have been found in patients with chronic tension-type headache (CTTH) for the first time. Pain processing areas such as dorsal rostral and ventral pons, anterior cingulate cortex, anterior and posterior insular cortex, right posterior temporal lobe, orbitofrontal cortex, para hippocampus bilaterally, and the right cerebellum were found to have decreased grey matter in patients with CTTH compared with control subjects and patients with medication overuse headache [56, 57].

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