Symptomatic headaches

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This paper is aimed to discuss some aspects of so-called symptomatic or secondary headaches with particular reference to the diagnostic criteria proposed by the IHS Classification Committee on headache disorders, cranial neuralgias and other head pain. Symptomatic headaches, in fact, represent an heterogenous group of conditions, sometimes with relevant clinical importance as warning symptoms of major intracranial pathology, sometimes benign in nature and with ill-defined clinical pictures and unclear relationship with the causative factor or event. It is therefore important to establish general principles for a more systematic approach to the problem of this group of headaches, also considering that some particular forms of secondary headaches may be viewed as reliable "in-vivo" models for pathophysiological investigation in head pain.

Key Words: symptomatic headaches — classification — haemorrhage — trauma — hormones.

Introduction

With the introduction of the Diagnostic Criteria estabilished by the IHS Classification Committee, [17] a significant improvement has been obtained in the clinical management of headache disorders. Operational criteria, in fact, even if representing a compromise between sensitivity and specificity, have definitely contributed to increase the scientific level of investigation in this field, for many years limited by a controversial taxonomy based on descriptive criteria as well as by more or less reliable theories on pain generation.
During the last years, due to the progress of research on pathophysiology and neuropharmacology, it has also been possible to develop and validate diagnostic and therapeutic guidelines for migraine headaches and to increase as well our knowledge on some relevant aspects about the pathogenesis and treatment of cluster and tension headache forms.
Besides primary headaches and cranial neuralgias, the IHS Classification system takes into consideration the so-called "miscellaneous" headaches (unassociated with structural lesion) and the heterogeneous group of the Symptomatic or Secondary headaches [17]. In the first group some particular benign headaches are listed coupling enough definite clinical characteristics (pain quality/duration) with peculiar precipitating/aggravating factors: headaches from cold stimulus, external pressure, cough, exertion, sexual activity. On the other hand, a large number of symptomatic headaches are characterized by variable headache pictures sometimes superimposable to primary forms (migraine-like, tension-like, etc.), sometimes less defined in terms of pain characteristics and associated phenomena (not fulfilling specific diagnostic criteria) but well identifiable for other aspects (time profile/cause-effect relationship with factors and events), some other times inconsistent for classification and diagnosis due to lack of specificity and poor or very poor clinical importance: headache as non-prominent symptom among those qualifying a syndrome, such as post-traumatic syndrome [1, 6] or pre-menstrual syndrome]15]. Therefore, in the view of a revision of IHS diagnostic criteria, some firm points must be stated when considering a symptomatic headache form for inclusion in this classification system: a) head-pain symptoms must be relevant and consistent for a diagnosis of headache, cranial neuralgia or other head pain; b) the above conditions should be of clinical importance in the con-

TABLE I. *Headache of neurosurgical interest.*

Pathogenesis	Causes
Meningeal irritation	Subarachnoid hemorrhage (ruptured aneurysms or AVM's, intraparenchymal hemorrhage, traumatic injury), Meningitis, Encephalitis, Iatrogenic (neurosurgical operations, post-pneumoencephalography, post-mielography).
Increased intracranial pressure	Hematomas, Tumors, Hydrocephalus, Thrombosis of venous sinus, Cerebral edema.
Decreased intracranial pressure	Iatrogenic (post-lumbar puncture), CSF-fistulae.
Vasodilatation of intracranial vessels	Post-seizures, Post-traumatic, Cerebro-vascular deficiency.
Focal lesion of the brain	Traumatic mass or processes occupying space with tension of periostium.

text of the diagnostic process aimed to demonstrate an underlying/causative disease or pathological condition (see headaches associated with vascular and non-vascular intracranial disorders); c) the concepts of "cause-effect" and "time-relationship" should be considered in a broader sense and given different levels of probability. Thus, symptomatic headaches remain open to further epidemiological, clinical and experimental investigation not only for their importance in the medical practice, but also for the opportunities they offer as "in-vivo" models of head pain syndromes in relationship with demonstrable causes and reproducible mechanisms.

In this perspective the present paper will consider only some particular forms of symptomatic headaches. Those associated with intracranial pathology of neurosurgical interest will be discussed in terms of epidemiology and differential diagnosis due to their role as "warning symptoms" of acute vascular events such as subarachnoid haemorrage. Provocation or worsening of migraine syndrome in relation to sex hormones, on the other hand, is also worth discussing for the pathophysiological implications, despite the inclusion of this group among the list of "headaches associated with substances" (8.5.1 - IHS Classification) is still matter of debate. Finally, post-traumatic headaches will be considered for their impact on different branches of clinical medicine as well as for the speculative interest of peculiar pain generating mechanisms [16].

Symptomatic headaches of neurosurgical interest

The pathogenesis of the headache of neurosurgical interest mainly depends on meningeal irritation, variation of the intracranial pressure, vasodilatation of intracranial vessels or focal cerebral injury. Headache of neurosurgical interst may be classified in five main groups (Table I). Headache has always been considered the typical symptom of onset of subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysms. The incidence of headache as warning sign in SAH is about 50%. The headache is short lasting and may be associated with vegetative disturbances (nausea, vomiting), stiff neck, syncopal episodes, and temporary sensitive and/or motor deficits. The more frequent warning sign is the diffuse headache (25%), due to a minor leakage, while focal headache (18%), ocular and/or facial pain are related to stimulation of the sensitive terminations of the arterial and/or aneurysmatic wall caused by small hemorrhagic infiltration. Besides, the distension of the aneurysmatic sac may contribute to the symptoms, by means of the periarterial receptors stimulation [29]. Diffuse headache is present in 32% of cases during a stroke episode, while severe headache in occipital region is present in 21% of the cases, and unilateral headache in 8% of the cases. The onset of the headache may or may not be associated with a brief loss of consciousness, nausea and/or vomiting, focal neurological deficits (including cranial nerves palsy), or stiff neck. The signs of meningeal irritation follow hemorrhagic stroke event with onset from 6 to 36 hours after stroke [30]. Headache is rarely absent: it is the case of hemorrhage in the cerebral parenchyma and producing loss of consciousness before the blood spread in the subarachnoid space. Headache in also absent in cases of pure subarachnoid hemorrhage with abrupt loss of consciousness [28] Cerebral vasospasm has a typical temporal course, with onset 3 to 5 days after the hemorrhage, maximal vessel narrowing at 5 to 14 days, and gradual resolution over 2 to 4 weeks. Cerebral vasospasm, increasing intracranial pressure due to ischemic lesion and to associated cerebral edema, increases the intensity of headache, eventually associated with focal or generalised symptoms and signs. The prevalence of headache, as warning sign of artero-venous malformation (AVM's), varies from 5% to 35% [40].

TABLE II. *Timing of migraine attacks in 116 women (the total percentage obviously exceeds 100%, as some patients reported attacks in more than one phase).*

Timing	Cases%
premenstrual phase	75.9%
during menstruation	53.4%
immediately after menses	44.8%
ovulation	9.1%

AVM's and intracranial aneurysms share the same physiological mechanism (minor leakage) but in AVM's the intracranial pressure in venous sinuses play a major role. The majority of patients affected by AVM's present with a long time history of headache, either migraine-like or more frequently "cluster"; but the duration of the attacks is shorter than migraine-like and/or "cluster", with long asymptomatic intervals (even years) between the attacks. The side and the localization of the attacks are always the same. About the AVM's with dural localization, the patient fells a pulsated headache, associated to sensation of "bruit" in the site of the shunt.

Increased intracranial pressure causes compression and dislocation of the vascular, meningeal, and cerebral structures. The venous system is the first compromised structure, and the subsequent venous stasis produces an increased in systemic blood pressure to support an adequate cerebral blood flow. Consequently the systemic blood hypertension induces an increase in the CSF-pressure. This increase is often secondary to processes space occupying of any nature, that obstruct the regular flow of the CSF.

The headache caused by the traction or dislocation of the vascular and meningeal structures is the classical symptom in the cases of intracranial hypertension; other signs are: vomit, papilledema, VI cranial nerve palsy and mental deterioration. Theoretically the intracranial tumours that do not obstruct the regular flow of CSF nor cause traction and/or dislocation of large intracranial vessels, may become of voluminous dimension, producing signs of intracranial hypertension and focal signs, preceding the headache. Nevertheless the headache is the first symptom at diagnosis in about 40% of the patients affected by malignant glioma. Moreover an important problem is the coexistence of perilesional edema. Whatever the space occupying processes that produces the intracranial hypertension syndrome (hematomas intra and extra cerebral, tumours, abscesses, thrombosis of cerebral sinus, etc.), the formation of edema increases much more the intracranial pressure, with worsening of symptoms. The formation of cerebral edema is the most important factor that conducts to intracranial hypertension. Cerebral disease more common associated with edema are: intracranial tumours, abscesses, traumatic injuries, ischemic and hemorrhagic events; seizures, systemic hypertension; acidosis and hypercapnia are rare causes. The presence of edema produces traction and dislocation of cerebral vessels which being sensitive to pain, causes headache [28].

The lumbar puncture causes subtraction of cerebrospinal fluid (CSF) from the subarachnoid space. This manoeuvre upsets the mechanism that permits brain to be suspend in a closed box (intracranial hypothension). The brain leans on the skull base, causing traction on vessels of the base, with onset of the headache. Same mechanism is responsible of the headache following post-traumatic CSF-fistula or iatrogenic fistula (trans-phenoidal approach) too. The introduction of air in the subarachnoid space (pneumoencephalography), of contrast medium (mielography) or of blood (surgical operation) provokes an inflammatory reaction sometimes very serious, with headache (iatrogenic headache), stiff neck, photophobia, and vomiting, mimicking bacterial meningitis.

Migraine and sex hormones

Epidemiological investigation has clearly demonstrated the crucial importance of sex hormones in modulating the clinical expression of migraine syndrome during the different phases of female life course. The attempt of understanding estrogens and progestins interference with those CNS structures and activities involved in the pathogenesis of migraine attacks is therefore of great speculative and practical importance.

Migraine develops most frequently in the 2nd decade in women, peaking at menarche [32, 9]; migraine attacks are linked to the period of menses in 60% of women, and occur exclusively in this period (true menstrual migraine) in 14% [23]. Migraine may worsen in the first trimester of pregnancy; many women become headache-free during later pregnancy, but 25% have no change [33, 26]. Menstrual migraine typically improves with pregnancy, perhaps due to sustained high estrogen levels [33, 26]. Migraine frequency decreases with advancing age, but may either regress or worsen at the menopause [13, 43]. Hormonal replacement with estrogens can exacerbate migraine and oral contraceptives (OCs) can change its character and frequency [18]. Changes in the headache pattern with OCs use and during menarche, menstruation, pregnancy, or menopause are related to changes in estrogen levels [3, 41, 21]. Menstrual migraine in particular offers a model to support this hypothesis.

As seen in table II the timing of migraine attacks in 116 women was distributed in a period around the menstruation and ovulation [15].
Normal menstrual cycle functioning requires the coordinated activity of the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH), the pituitary, which secretes glycoproteins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), the ovary, which secretes estrogens and progesterone, and the endometrial lining of the uterus, which responds to estrogen and progesterone. Under the control of norepinephrine, serotonin, the opioids, and other neurotransmitters, the hypothalamus secretes GnRH in a pulsatile manner, which stimulates pituitary LH and FSH. This in turn stimulates secretion of ovarian estradiol and progesterone, which feed back at the pituitary to modulate the relative amounts of LH and FSH, and at the hypothalamus to regulate GnRH. Estrogen exerts negative feedback regulation on the pituitary [11, 22]. On the other hand, sex hormones have direct CNS effects, binding to receptors in opiatergic and other neurons in the area of the brain responsible for reproductive behavior and gonadotropin release [24]. Estrogens increase the number of progesterone and muscarinic receptors and modulate 5-HT2, and beta adrenergic receptors [4]. Estrogen withdrawal increases the number of dopaminergic receptors [14]. Progesterone modulates the estrogen effects on 5-HT1 and 5-HT2 receptors. Estrogens also affect the peripheral nervous system, increasing, in rats, the size of the receptive fields of trigeminal mechanoreceptors [2].
Also the frequency and character varations of migraine under OCs administration are possibly related to fluctuations in estrogen level and OCs-induced migraine is therefore an interesting clinical model.
OCs most commonly used contain combinations of synthetic estrogen and progestogen taken 21 days each month. Somerville et al [34] reported that the headache of menstrual migraine occurred during or after the simultaneous fall of estrogens and progesterone, and that giving estrogens premenstrually delayed the onset of migraine but not menstruation [34]. In contrast, progesterone administration delayed menstruation but did not prevent the migraine attack [35]. Somerville concluded that estrogen withdrawal may trigger migraine attacks in susceptible women. Estrogen-withdrawal migraine requires several days of exposure to high levels of estrogen [36]. When he used an erratic delivery system of long-acting estrogen implants to suppress migraine, his patients developed irregular bleeding and headaches associated with fluctuating estrogen levels [37]. The fluctuation in estrogen levels produces many biochemical changes that may be relevant to the etiology of menstrual migraine.
Estrogens and progestins in combination, as in OCs interfere with the midcycle gonadotropin surge at the hypothalamic and pituitary levels, preventing ovulation [42]. OCs can therefore induce, change, as well as alleviate headache [3]. OCs can trigger the first migraine attack, most often in women with a family history of migraine [18, 3, 27]. New-onset migraine usually occurs in the early cycles of OCs use, but can occur after prolonged OC usage [27]. Stopping the OCs may not bring immediate headache relief; there may be a delay of 1/2 to 1 year, or no improvement [18, 8].
Headache associated with OC use or menopausal hormonal replacement therapy may in part be related to periodic discontinuation of oral preparations of the sex hormones. Thus, the effects of estrogen on the genesis of headache may be a result of a mismatch between the ovarian sex hormones cycles and the inherent rhythm of CNS estrogen-sensitive neurons, including perhaps the serotonergic pain-modulating systems.
In a review on the relationship between migraine and the pill, Facchinetti and co-workers [10] took into account factors such as types and doses of the various steroid compounds, length of administration and populations studied. In fact, discontinuation of pill intake due to headache was probably more frequent when compounds used were progestogens only. Beside, the type of preparation, population studied was also important: the progesterone pill alone in northern countries did not induce noticeable headache, but the same drug, at the same dose, induced headache in 30% of women selected from a city population in Chile [10].
The speculative importance of this topic also extends to Premenstrual Syndrome, which includes menstrual migraine as a frequently component, along with various somatic, psychic and behavioural complaints. In this view, headache and migraine related hormonal variations may find in premenstrual headaches and in OCs or estrogen replacement headaches an important model for in-vivo studies.

Post-traumatic headache

The frequency of post-traumatic headache varies widely in the various reports from the literature, but there is enought evidence to confirm its strict relationship with minor rater than major head trauma together with the scarce specificity of the clinical picture, the poor prognostic value of event-related factors (loss of consciousness/duration of amnesia/circumstances and dynamics of im-

pact) and premorbid personality [1, 5]. Both headache and the set of symptoms constituting the so-called chronic post-traumatic syndrome, on the other hand, have been subjected to revision with particular regard to their classification and pathophysiology [6, 12, 19, 20]. In fact, for many years head pain of post-traumatic origin, particularly when continuous and long-lasting, has been attributed to conversion mechanisms (post-traumatic neurosis).

However, an overwiew of human studies on trauma-induced alterations of dopaminergic and serotoninergic systems together with the results of our previous studies on PRL secretion rhythms in patients with post-traumatic headache [31] may substantiate the hypothesis that even minor traumas are capable of inducing subtile anatomical and functional alterations in the CNS.

Delayed neuronal damage and dysfunction of neural transmission can be responsible for the development of an acquired headache susceptibility as well as for the long-lasting changes of personality and cognitive performance frequently observable in these patients.

Among the chronic sequelae of minor head injury, headache is the most frequently complaint, ranging from 70-80% of the cases [1].The prevalence of post-traumatic headache among symptomatic headache forms is 4% [25], with an higher incidence for females vs males (49% to 30%) as reported by studies on large cases-series seen at 9-12 month-intervals from the acute event [5, 6]. The International Classification of Headache [17] distinguishes between acute and chronic from respectively, with a time limit for onset of 2 weeks and a minimum duration of over two months for the chronic forms.

The clinical characteristics of headache resemble most often those of migraine and tension type, even if in many cases head pain does not strictly meet the diagnostic criteria for any form of primary headache. Preexistence of a primary headache does not seem to be a relevant factor for predisposition to a chronic post-traumatic headache nor headache charcteristics seem to be influenced by previous headaches. Worsening of a preexisting headache after injury is commonly labelled with reference to the pre-existing headache form, while head pain developing after injury may be correctly described by using the diagnostic criteria for primary headache with the specification of the post-traumatic condition.

The limit of this classification, however, is represented by the fact that in many cases post-traumatic headaches do not reproduce any form of primary [spontaneous] headache. According to Bussone at al. [6] only 3% of post-traumatic headaches fit the criteria for migraine and 16% those for tension headache. Some acute and post-acute post-traumatic headaches of the migraine type, however, have been described for their importance as a model of spontaneous headache: footballers migraine and other forms frequently reported among sport-practicing young inividuals (post-traumatic migraine). Besides migraine and tension headache, other head pain syndromes may originate from head injury, such as temporo-mandibular joint disease, trigeminal neuralgias and unilateral headaches associated with oculosympatetic paresis.

Neuroimaging and neurophysiology do not help in investigating functional symptoms and the diagnostic workup often requires different tecniques to assess eventual associated dysfunction in behavior and cognition. The evaluation of these patients should therefore include neuropsychological investigation and a complete assessment of personality and affective status in order to provide appropriate rheabilitation and to ease the return to normal social and working activities.

Different problems originate from minor injury to the cervical spine. Also this condition (whiplash injury) is accompanied by significant headache affecting about 80% of patients during the post-acute phase (1-2 months) and is followed by more or less chronic headaches lasting for months or years, frequently accompanied by other symptoms (vertigo/neck stiffness/anxiety/depression and insomnia) commonly reffered to as "chronic sequelae of uncomplicated whiplash injury" [1, 39]. For some of these headaches a clear time-relationship between traumatic event and pain onset is not demonstrable, but the number of cases with headache of cervical origin and a positive history of previous minor neck trauma is very significant for pathogenetical considerations (cause-effect relationship).

This seems particular true for so-called cervicogenic headache, an entity recently included in the IASP Classification [7]. Cervicogenic headache [7, 38] is a unilateral headache, frequently episodic at the beginning and later chronic or fluctuating, characterized by pain originating in the neck, reduced range of motion and mechanical precipitation of attacks by neck movements or by external pressure over the upper cervical or occipital region on the symptomatic side.

Pain arising from the neck may spread to ipsilateral anterior regions and be referred to shoulder and arm, omolaterally. A relevant characteristic of pain is the lack of response to anti-migraine drugs and the selective response to anesthetic blockades (occipital nerves/C2 - C3 roots) which are of diagnostic importance.

Table III reports the results of a retrospective analysis of n. 38 cases with unilateral headache symptoms fulfilling the two major criteria for cervicogenic headache. Pain characteristics are sig-

TABLE III. *Main characteristics of cervicogenic headache (n. 38 cases).*

Pain location		Associated symptoms	
Frontal	12	Nausea/vomiting	16
Orbital	35	Photo/phobia	31
Parietal	9	Tinnitus	5
Temporal	32	Dizziness	18
Occipital	8	Lacrimation/rhynorrea	5
Neck	38	Eye-lid edema	12
Precipitation/facilitation of attacks:			
by neck movements	n. 11/38		
external pressure/sustained posture/exercise	n. 37/38		

TABLE IV. *Cervicogenic headache (n. 38 cases): personal history of head/neck trauma and interval between the event and headache onset.*

	N. cases	time-interval*
Major head trauma	—	—
Minor head trauma	5	2-5 months
Major cervical trauma	6	1-16 months
Minor cervical trauma	11	4-21 months
Minor and major head and neck trauma	3	1-14 months

nificantly different from those of migraine and tension headache and the temporal pattern is chronic or chronic-fluctuating in 84% of the cases. Table IV demonstrates that in n. 25/38 cases a minor head/neck injury is present in the personal history of these patients, with a variable temporal relationship between the event and the headache onset. This observations confirm the importance of minor injury in pathogenesis of cervicogenic headache and stress the role of whiplash injury as a pathogenetic model for this form of headache. On the other hand, it is known that degenerative alterations of cervical spine structures are detectable with higher frequency [39] in patients with previous whiplash injury versus the normal control population, even if routine examination fails in demonstrating those minor alterations of disk, ligaments and articular facets that can represent the origin of postural abnormalities and consequent pain symptoms.

Sommario

Scopo del lavoro è di discutere alcuni aspetti relativi all'inquadramento nosografico delle cosiddette cefalee sintomatiche o secondarie, con particolare riferimento alla Classificazione della International Headache Society (IHS), attualmente in corso di revisione. Le cefalee sintomatiche rappresentano infatti un gruppo eterogeneo di disordini e condizioni talvolta di grande rilevanza clinica, come nel caso delle cefalee sintomatiche di patologia intracranica vascolare e non vascolare. Peraltro, rientrano invece in questo capitolo quadri clinici mal definiti (aspecifici) e con incerta relazione causa-effetto con i vari fattori ed eventi con i quali un quadro di cealea o di dolore cranio-facciale si associa. Esiste poi un'importanza speculativa per le cefalee secondarie, rappresentata dalla possibilità di considerare alcune forme quali modelli in vivo per approfondire i meccanismi patofisiologici alla base della produzione del dolore cefalico.

Sulla base di queste considerazioni vengono discusse, rispettivamente, le cefalee di interesse neurochirurgico (come sintomi premonitori di patologia maggiore intracranica), le cefalee secondarie a variazioni degli ormoni sessuali nel corso della vita riproduttiva e nel caso della somministrazione di estroprogestinici, le cefalee post-traumatiche per il rilievo fisiopatologico che assumono nei confronti di alcune forme di emicrania e di cefalea cervicogenica.

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