CLUSTER HEADACHE: FROM CLASSIFICATION TO CLINIC AND TREATMENT

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Cluster headache is a rare and very severe episodic primary headache that has been recognised for many years among the earliest known descriptions appearing in Gerhard van Swieten's medical textbook:

"A healthy robust man of middle age [was suffering] troublesome pain which came on every day at the same hour spot above the orbit of the left eye, where the nerve emerges from the opening of the frontal bone: after a short time the left eye began to redden and to overflow with tears, than he felt as if his eye was slowly forced out of its orbit with so much pain, that he nearly went mad. After a few hours all these evils ceased and nothing in the eye appeared at all changed".

This description fulfils the International Headache Society diagnostic criteria for cluster headache. Before the term *cluster headache* was widely used, the disease was known by a large number of names, with perhaps the most remarkable understatement being that Sir Charles Symons who called it a *particular variety of headache.*

In this way cluster headache can be defined as a severe headache pain with particular characteristics of sex, age, position, autonomic site and difficulty in treatment. Perhaps the over-riding problem in acute cluster headache is that the attacks come on rapidly and reach a peak very quickly so that therapy to be of any value must be rapid in onset and thus oral preparations used in migraine may not be effective.

In 1988 in Toronto Prof. Goasby presented a new reclassification of headache instead of International Headache Society (IHS) classification.

According to IHS classification, cluster headache can be of different type:

- cluster headache periodicity undetermined;
- episodic cluster headache: at least two periods of headache (cluster periods) lasting (untreated) from seven days to 1 year, separated by remission of at least fourteen days;
- chronic cluster headache: as episodic cluster headache, but absence of remission phases for one year or more with remission lasting less than fourteen days.

Cluster headache is characterised by: severe unilateral pain, orbital/superorbital site - different from migraine pain, which is always lateral and pulsating -, pain may spread to nose, jaw.

The autonomic site has to be considered when you diagnose migraine pain as opposed to cluster headache. The characteristics are:

- conjunctival injection and lacrimation,

- nasal congestion and rinorrhea,
- forehead and facial sweating
- miosis, ptosis, eyelid oedema.

Differential diagnosis has to be made with:

- chronic paroxysmal migraine in which pain lasts from 2 to 45 minutes, frequency high as 30/24 hours and there is great female predominance;
- temporal arthritis;
- meningiomas;
- A-V malformations;
- cerebral aneurysms;
- post-traumatic pain.

The epidemiology is a very important problem. The prevalence is very low within the whole headache pathology. It ranges from 0,009-0,4%. The prevalence in Italy is about 0,7%, according to D'Alessandro and S. Martino. The incidence is 15,6 in 100,000 men per year and the risk of illness is thirteen times more probable in first grade relatives.

Cluster headache is a severe pain difficult to treat. From time to time, the strength of the pain induces us to try anthalgic techniques which may give considerable results but at the same time can provoke dangerous side effects.

Our concluding suggestion is to eliminate every type of invasive technique against the sphenopalatine ganglion and to promot to relieve the symptoms of cluster headache. They are superficial compression of the portal artery, common carotid compression, to be sit or standing, head positions, hard physical efforts, alcohol intake.

We should consider cluster headache as hypothalamic hypothesis, which includes alteration of circadian rhythm of prolactine, cortisole, melatonine, beta-endorphin; alteration at response from TRH to TSH, from CRF to CORTISOLE, to CORTISOLE to HYPOGLYCEMIA, from MCCP to CORTISOLE and PROLACTINE. So we can conclude that the alteration of suprachiasmatic hypothalamic nuclei and the hypothalamic pathway originates from and is regulated by the circadian rhythm.

It is possible to see the difference between the cluster headache and migraine according to May and Goasby, with Positron Emission Tomography (PET). PET is a neuroimaging technique that allows measuring the regional cerebral blood flow. This parameter is an index of synaptic activity.

In-patients with cluster attacks during the acute pain state, activation was seen in the ipsilateral inferior hypothalamus nuclei. These areas are well known as pain sites. Previous observation was not detected in-patients with migraine.

The dysfunction begins in the hypothalamus, which subsequently activates the trigeminal pathways through the sphenopalatine ganglion and the internal carotid arterial with the sensibilization of the dura mater. Hypothalamus is likely to be the site of a dysfunction that activates the trygeminal pathways producing pain and associated symptoms.

The treatment of acute attack:

- Oxygen 100%: it is necessary an inhalation of 7-10 l/min for 5-10 minutes as soon as the symptoms appear, patient should sit down, the facial mask is to be preferred to nasal cannula, avoid hyperventilation, this treatment is well tolerated and could be used at patient's home;
- Dihydroergotamine iv 0,5-1 mg: given iv is effective, it presents fewer problems than ergot, (DHE nasal spray 1 mg., half the recommended dose for migraine);
- Ergotamine 0,25 mg.: given iv or im is effective (70-80%), the same adverse events as for os, it lacks of well controlled clinical trials, it is necessary to be aware of adverse events and abuse, some patients respond to rectal ergotamine;
- Sumatriptan 6 mg. subcutaneous: this is the most effective treatment for pain relief. It gives fast relief in 15 minutes (74% in double blind study), the start of relief is from 5 minutes onwards, current device is easy to use, typical adverse events (triptan syndrome);
- Topical anaesthetic: there are few cases reported in detail, lidocaine 4-6% nasal drops (1 cc), cocaine is not utilised because of its addictive potential;
- Ergotamine derivatives in episodic cluster: ergotamine tartrate (1-2 mg./die for max 6 week), it can present problems of adverse events due to abuse/overdose, if the attacks appear at fixed hours ergotamine 1 mg. 1-2 hours before the expected onset, if the attacks come during the night, it is indicated to use the dihydroergotamine, 1 mg. in the evening;
- Methysergide: 3-6 mg./die (not more than 3-6 months), it is a semisynthetic type of ergotamine, acts as 5-TH antagonist, it is effective in episodic ($\approx$ 70%), but not in chronic cluster, the severe side effects are fibrotic reactions (pleural, peritoneal, cardiac valvular), muscle cramps, diarrhoea, nausea, abdominal discomfort, the contraindications are blood hypertension, cerebral and peripheral vascular diseases;
- Verapamil (240-360 mg./die) is the first line drug, it is an antagonism for Ca^{++} channels, 5-HT, NorAdr $\alpha 2$ and β, it is in competition for dopamine D2 receptors, the effective rate is about 70%, the main side effects are oedema, dizziness, nausea, fatigue and hypotension, finally the drug interactions are increasing in lithium serum levels and decreasing in carbamazepine serum levels;

- Transdermal clonidine (0,2 mg./die for week) is an α2 adrenergic presynaptic agonist and reduces the sympathetic overflow from brain stem nuclei, the side effects are tiredness and hypotension;
- Lithium (300-900 mg./die) is effective in chronic, but not in episodic cluster, it reduces the intensity and frequency, but induces severe side effects: tremor, lethargy, thirst, nausea, blurred vision and vomiting. It presents some contraindications as renal and cardiac impairment, GI disorders, Addison disease and pregnancy. The normal range of lithium blood levels is 0,5-1,0 mEq/l (1/week for first month, then 1 for month). Lithium induces some metabolic effects:
  - increase of 5-HT release with increased blood levels and urine metabolite;
  - alteration in catecolamines reuptake and pre-synaptic storage;
  - increased enkefalines availability;
  - increased uptake and cell glucose concentration;
  - interference with erythrocytes APT Na-K related;
  - increased Mg, K, Ca (?).
- Corticosteroides have an anti-inflammatory action and produce suppression of hypothalamus-hypofisis-surrenal pathway. In decreasing doses are indicated Prednisone and Dexamethazone. The contraindications and adverse effects are: glaucoma, immunitive disorders, mental diseases, hepatic, cardiac and renal impairment. It is necessary to use some precautions as to control blood pressure and electrolytic and to check GI.

There are some other therapies that are not yet validated:

- nasal spray Lidocaine (4%);
- nasal Capsaicine (300 MCG/die);
- Somatostatine (e.v. infusion);
- mg sulphate (e.v. infusion);
- hyperbaric oxygen (2,5 atm per 30 minutes);
- histaminic desensitisation ;
- Cyproeptadine;
- histamine antagonists at H1 and H2;
- Pizotifene (1,5 mg/die);
- beta-blockers (Propranolol);
- Lisuride (0,05-0,5 mg/die);
- Indomethacine (150 mg/die);
- Nimodipine (60-120 mg/die);

- Sodium valproate (600-1500 mg/die);
- Melatonine (5-10 mg/die).

Symptoms similar to cluster headache were observed by Vail and described as Vidian Neuralgia or *"irritation of an inflammatory process in the sphenoid sinus upon the vidian nerve*[1]*"*. Slauder when referring to *"sphenopalatine ganglion neuralgia gave it the name of Sluder's neuralgia*[2]*"*.

Kithelle et coll.[3] suggests that: *"the primary mode of afferentation of pain in cluster headache lies in the pterigomaxillary fossa"*. This observation is supported by: *"the effectiveness of a solution of hydrochloride cocaine [that] suggest the pain in cluster headache originates from the pterigomaxillary fossa area"*.

Other observation that confirm the sphenopalatine fossa involvement were made by Hardebo[4]: *"strong evidence exists that sphenopalatine ganglion and this branches that pass through the ganglion itself into the thin pterigo-palatine fossa are involved in the pathogenesis of cluster headache"*.

Hardebo reaches the same conclusion in the sense that many nervous fibres crossing the pterigo-palatine fossa are involved in the pathogenesis of cluster headache.

During migraine and cluster headache attacks there is a clear presence of symptoms related to an alteration in the autonomic system activity. This alteration is characterised by a parasympathetic hyperactivity (system-specific with vascular brain trunk).

Parasympathetic neurotransmitters include substances that trigger the inflammation, acethilcoline, able to stimulate the C-sensitive fibres.

Via the palatine ganglion activation, the parasympathetic stimulation produces a sterile inflammation in rat dura mater[5].

In the cluster headache pathogenesis we could pay attention to:

- trigemino-vascular innervating (Moskowitz, 1972);
- sphenopalatine ganglion;
- pterigo-palatine fossa (Hardebo, 1955);
- sinus cavernous and ophthalmic afferent veins;
- innervating of plexus pericarotideal in the intracavernal pathway of internal carotid (Sjastad, 1996).

The parasympatic activation of fibres constricting to sphenopalatine arterial produces:

- Compression against the sphenopalatine foramen that presents wide variation (Nikolic, 1968);

- The connection between parasympathetic and afferent sensitive fibres in the ascending trigeminal nucleus could be responsible for triggering abnormal circle pathways that could explain the wide range of pain during the attacks.

It not necessary to detect the site of the primary trigger factor responsible for cluster headache.

We suppose that blocking the increased parasympathetic sensorial fibre activity would produce a good result.

Unfortunately we should remember that 4-15% of patients affected by cluster headache don't respond to the therapy. We can present some observations about alternative treatment during a cluster headache attack resistant to drug treatments:

- cocaine solution injection (Barre, 1982);
- local infiltration with Lidocaine (Robbins, 1985);
- alcoholic neurolisis (Devogher, 1981);
- cryosurgery (Cook, 1978);
- gamma knife treatment (Ford, 1988);
- radiofrequency neurolesions (Sanders, 1997);
- surgical treatment, neurovascular decompression via naso- cranic base (Bonaccorsi, 1995);
- epicranial blocks in headache treatment (Caputi, 1995).

During 10 years of clinical experience we have treated 5 cases of cluster chronic headache with microdecompression of Gasser ganglion technique, we obtained pain resolution in 4 cases for 28 months and 1 case for 1 year.

In this last patient the technique was repeated twice (the compression was extended from 7 minutes to 9 minutes). This produced a small haemorrhage, resolute with medical therapy.

This method may be used without the danger of deafferentation.

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[1] Vail, H.H.: Vidian Neuralgia. Ann Otol Rhin Laring, 1932.
[2] Barre, 1982.
[3] Kithelle, 1983.
[4] Hardebo et al., Headache, 1987.
[5] Henry et al., 1966.

DOLORE NEUROPATICO

E' UNA MODALITA' SENSORIALE CHE NON RISULTA DALLA ATTIVAZIONE PERIFERICA DEL NOCICETTORE (TRASDUZIONE) E CONSEGUENTE SEQUENZA DI TRASMISSIONE - MODULAZIONE - PERCEZIONE, COME ACCADE PER IL DOLORE NOCICETTIVO (SOMATICO O VISCERALE).

E' UN DOLORE SENZA NOCICEZIONE; AD ESSO NON CORRISPONDE A LIVELLO TISSUTALE UN VERO E PROPRIO PROCESSO ATTIVO DI TIPO LESIONALE CHE NE GIUSTIFICHI LA PRESENZA O ENTITA'.

NON E' SOSTENUTO DA UN DANNO CONTINUO DEL TESSUTO E PERSISTE A LUNGO DOPO CHE I PROCESSI LESIVI E RIPARATIVI SONO TERMINATI.

E' UN DOLORE DOVUTO ALLA SOLA PERCEZIONE CON ANOMALA INTERPRETAZIONE DEI SEGNALI AFFERENTI AL MIDOLLO.