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Cluster headache and its variants

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Introduction

When I first joined Lord (then Dr) Walton's unit in September of 1962, I was immediately impressed not only by his unique expertise in muscle diseases, but also by his encyclopaedic knowledge of medicine, and his versatility. Not surprisingly this caused digressions which strayed from the myofibril; one such diversion took him and my colleague, John Balla, into the field of cluster headache or migrainous neuralgia as it was then called in England.[1] Years later, Lord Walton had remained faithful to myology, Balla branched into the methodology of medical learning and Bayesian theory, and I became entangled in the more banal and mundane problems of headaches.

For many years cluster headache was known as periodic migrainous neuralgia of Wilfred Harris, erythroprosopalgia of Bing, histaminic cephalgia, sphenopalatine neuralgia, Vidian or Sluder's neuralgia and, in the USA, Horton's headache. The condition was thought to be a variant of migraine. However, since there is no specific diagnostic test for either condition and their aetiologies remain uncertain, the nosology remains confused. Opinion has shifted from regarding cluster headache as a migraine variant, and I shall consider and compare their differences which are important. Essentially we are dealing with clinical phenomena,[2] because although a variety of laboratory abnormalities have been shown to accompany both types of attacks, no one of them is of causal importance; many are epiphenomena. The diagnostic criteria of the International Headache Society are given in Table I.

Historical aspects

Priority for description of cluster headache or periodic migrainous neuralgia[3] is a source of polemic. Much depends upon the stringency of criteria applied. Hierons refers to Thomas Willis (1621-1675) who described 'a venerable matron who began to suffer every afternoon at 4 o'clock from recurring severe (cluster) headache'. In 1747 Joannes Christoph Ulricus Oppermann published his little acknowledged Dissertatio Medica Inauguralis, entitled 'Hemicrania Horologica' which may be the first account of the variant, chronic paroxysmal hemicrania.

Benjamin Hutchinson's description (1822) of 'neuralgia spasmodica' is often cited as the original account of cluster headache, with attacks every 24 hours, but lasting for several hours. The nature of these attacks is dubious, and some were probably tic douloureux.

Table I Diagnostic criteria of cluster headache*

(A) At least five attacks fulfilling B-D
(B) Severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes untreated
(C) Headache is associated with at least one of the following signs which have to be present on the painful side.
  (1) conjunctival injection
  (2) lacrimation
  (3) nasal congestion
  (4) rhinorrhoea
  (5) forehead and facial sweating
  (6) miosis
  (7) ptosis
  (8) eyelid oedema
(D) Frequency of attacks: from one every other day to eight per day.
(E) At least one of the following:
  (1) history and/or physical and neurological examinations do not suggest other disorders associated with head trauma
  (2) history and/or physical examination do suggest acute post-traumatic headache, but it is ruled out by appropriate investigations
  (3) Such disorder is present, but cluster headache does not occur for the first time in close temporal relation to the disorder.

Episodic cluster occurs in periods lasting 7 days to one year, separated by pain-free periods lasting 14 days or more. Chronic cluster headache: attacks occur for more than one year without remission or a remission lasting less than 14 days.

*International Headache Society, Classification. Diagnostic Criteria. *Cephalalgia* 1988, **8** (Suppl. 7), 19-45.

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Romberg (1853) in his classic Manual records: 'painful sensations in the eye, confined to one side and excited by rays of light and visual effort... The pupil is contracted. The eye generally weeps and becomes red. These symptoms occur in paroxysms, of a uniform and irregular character, and isolated or combined with facial neuralgia and hemicrania.' Romberg's emphasis on the photophobia is incongruous with current concepts, but he was clearly observing a condition closely akin to cluster headache and may merit priority. Later accounts included Mollendorff's 'red migraine' and later, Sluder's 'neuralgia of the vidian nerve'. The condition is sometimes known as periodic migrainous neuralgia of Wilfred Harris, and in the USA as Horton's syndrome. Both men made signal advances in our recognition of this still underdiagnosed though curiously distinctive syndrome.

Clinical features

Pain of agonizing severity is the cardinal symptom. Attacks start at any age, but are rare in children. They last for 30–120 minutes, occurring usually once or twice every day for a period of about 4 weeks to 4 months. Total remission is then the rule, until the next cluster ensues months or a year or two later.[4] During the cluster, attacks often occur at night, commonly an hour after the onset of sleep; this pattern is maintained and the time switches when a shift-worker changes to daylight periods of sleep.[5] 'I can set my alarm clock by it'. Attacks also occur during the day, often at predictable times, but sometimes at random.

The pain is usually centred on one orbit. It is strictly unilateral for the duration of the cluster. Rarely it can change sides in a later bout. It may radiate to the face, jaw, neck and shoulder. Patients complain of deep boring pain of a severity greater than migraine; they may be reduced to tears, bang their heads on a wall, but more often pace the floor restlessly or wander outdoors to seek assuagement in the cold night air. This contrasts with the quest for stillness and darkness of the migraine victim.

The frequency builds up at the start and peters out at the end of the cluster. Vasodilators, notably alcohol, nitrites[6] and calcium channel blockers may precipitate attacks during the cluster, but not in phases of remission. The visual and sensory symptoms of classic migraine do not occur and vomiting is rare.

One of the hallmarks is redness and watering of the ipsilateral eye during the attack.[6] The nostril too may run or feel blocked. Swelling, dilatation and tenderness of the superficial temporal vessels are occasionally reported. Miosis with or without ptosis occurs in 20% of attacks and in about 5% a permanent partial Horner's syndrome persists. Table II summarizes the main clinical differences from the common and classical forms of migraine.

Differential diagnosis

Table III illustrates the main headache syndromes which mimic the disorder; most are identified by an adequate history without recourse to laboratory investigations. Occasionally typical cluster pain is symptomatic of a giant basal aneurysm or a

Table II Comparison of cluster headache with migraine

Cluster headache	*Migraine*
(1) An affliction of males (M:F 10:1)	Females more often (M:F 2:3)
(2) No aura	Visual/sensory aura of classic migraine present in 25% of patients
(3) Strictly unilateral distribution of pain	Pain often bilateral or, hemicrania on either side
(4) Pain duration usually 30–120 minutes	Longer, generally lasting 12–48 hours
(5) Family history usually negative	Positive family history of migraine in 70% of patients
(6) Headache occurs in daily attacks for 4–12 weeks	Single attacks with invervals of freedom
(7) During cluster, attacks occur 1–3/day; predilection for the hours of sleep	Attacks last 1–2 days often start on waking
(8) Total remission after a cluster, often 6–18 months	Shorter remission

Table III Differentiating features of syndromes simulating cluster headache

Differentiating features	*Syndrome*
Long duration, vomiting, periodicity	Common migraine (table)
Aura, duration, vomiting, periodicity	Classic migraine (table)
Jabs, triggers, frequency, rarely nocturnal	Trigeminal neuralgia
Progressive course, fits, focal signs, raised intracranial pressure	Brain tumours
Middle aged or elderly, precipitated by neck movement, no eye signs; restricted neck movements	Cervicogenic pain
Elderly, malaise, myalgia, inflamed arteries, high ESR	Cranial arteritis
Attack of shingles, post herpetic scarring and pigment; attacks throughout day and night	Post-herpetic neuralgia

cerebral angioma, but in most such cases there are atypical symptoms, a bruit or a progressive course which will arouse suspicion and thereby further investigation.

Variants

There are, first, two dubious entities: cluster headache preceded by classic migraine aura has been called 'cluster migraine'; and cluster headache with separate clusters of attacks of vertigo, tinnitus and deafness as in Ménière's syndrome, has been labelled 'cluster vertigo'.

'Chronic migrainous neuralgia' also called 'chronic cluster headache' is a genuine entity which constitutes about 10% of cases. Clinical features of each attack[1] are identical to those of typical episodic cluster headache. The difference is that the remissions which characterize the episodic form fail to occur. Since they fail to cluster, the term chronic cluster is a misnomer.[1,3] Those patients who have never experienced a remission but have chronic attacks from the outset are labelled 'primary chronic', those who start with episodic clusters but in a later attack have chronic persisting symptoms are labelled 'secondary chronic'. The features are seen in Table IV.

Chronic paroxysmal hemicrania was described by Sjaastad and Dale,[7,8] and is an uncommon variant with five distinctive features which separate it from the episodic type (Table V).

Aetiology of cluster headache

Any theory of causation must explain: the male predominance, the distinctive pattern of paroxysms in clusters, the unilateral and presumed vascular pain and the autonomic signs in attacks. Testosterone and other assays have shown only inconstant and variable changes in plasma hormones, and shed no clear light on the reason for the sex distribution. Between attacks there are no constant pathological changes in either intracranial or extracranial arteries or veins in this disorder. A vascular component of the pain is suggested by the precipitation of headaches by vasodilators, such as nitroglycerine and by the relief afforded by vasoconstrictors, such as oxygen and alpha-adrenergic drugs. Cerebral hyperperfusion, esp-

Table IV Chronic as compared to episodic cluster headache

(a) Daily attacks continue for more than 6 months
(b) The frequency of attacks may be increased
(c) Diminished response to ergot, methysergide and steroids
(d) Better response to prophylactic daily lithium salts

Table V Features of chronic paroxysmal hemicrania

(1) It occurs predominantly in females
(2) Attacks are more frequent, often 5–20 per day
(3) They are of shorter duration, usually from 3–15 minutes
(4) They respond almost invariably to indomethacin, 75–150 mg/day, but not to other non-steroidal anti-inflammatory drugs
(5) Some episodes appear to be triggered by neck movement.

ecially of grey matter has been shown by ^{133}Xe inhalation and carotid injections in small numbers of patients. Increased extracerebral flow has also been shown during attacks. The normal vasodilator response to CO_2 is reduced, but the response to O_2 is probably increased; these vascular regulatory responses contrast sharply with those in migraine. Not all workers have found these results; Krabbe, Henriksen and Olesen using single photon emission computerized tomography (SPECT) with ^{133}Xe inhalation in 18 patients[9] with headache induced showed no gross changes in cerebral blood flow but regional differences in basal central areas. In attacks there is extracranial vasodilatation mediated by parasympathetic activity via the greater superficial petrosal branch of the facial nerve. The afferent path for the pain lies in the trigeminal nerve whose central projections interact with periaqueductal grey matter, the site of central pain threshold monitors. Upstream projections alter cerebral blood flow and ultimately efferent discharge through the facial nerve.

There have been instances demonstrated where there is mural oedema of intracranial vessels, particularly the carotid syphon as in migraine.[10] In cluster headache, autonomic signs are the rule during attacks. Lacrimation is seen as parasympathetic excess, and a partial Horner's syndrome is evidence of a coincident sympathetic paralysis. A postganglionic (3rd neurone) Horner's syndrome[11] is present in up to a third of patients, implying a lesion of the pericarotid sheath or vessel wall. This is manifest by ptosis, miosis and an area of decreased sweating. In patients with residual miosis, installation of eye drops shows significant impaired dilatation of the pupil in response to OH-amphetamine (a noradrenaline releaser), and a supersensitivity to phenylephrine (a direct postsynaptic noradrenaline receptor).[12] There is also an impaired reflex sweating and flushing over segments of the forehead and cheek, induced by body heating. Doppler studies show decreased velocity of flow in the lateral supraorbital arteries (branches of the internal carotid) during attacks.

In a 'precluster period', plasma methionine–enkephalin levels rise dramatically, falling to basal values during episodes of pain. Leukotriene B_4, a mediator of hyperalgesia, vasoconstriction and plasma leakage is elevated at the onset of cluster headaches. There is also increased basophil sensitivity, degranulation and release.[13] It is not known whether these and other factors play a causal role in attacks or in the genesis of pain.

Treatment

No treatment which will prevent attacks or alter the natural history is known. Our efforts are aimed to suppress symptoms. Precipitating factors must be avoided, notably alcohol and where possible certain vasodilator drugs, such as nitroglycerine. A seasonal incidence and claims for attacks related to hard-driving life styles are seldom amenable to modification.

Ergotamine is the drug of choice.[3,6] In contrast to migraine it is given in *anticipation of each paroxysm*. This usually means a dose each night on retiring to bed to prevent nocturnal attacks, and additional doses during the day, one hour before current experience tells the patient an attack is due. If they are not 'clockwork', then 8 hourly doses are given. Tablets (Cafergot, Migril) are poorly and erratically absorbed; they are of little use. Suppositories containing 2 mg ergotamine are advised; half (1 mg) will suffice in many patients. Inhalation (Medihaler ergotamine 0.34 mg/puff) affords an efficient alternative, but careless handling may lead to overdosage. Rarely, patients need to inject themselves with subcutaneous ergotamine. Dihydroergotamine is an acceptable alternative taken as a nasal spray in dosage of 0.5 mg. Hypertension, coronary and peripheral vascular disease are relative contraindications. Treatment is generally very successful in aborting attacks and is omitted each weekend to see if the cluster has spontaneously ended. If headaches recur, a further week's treament is given; this trial continues until the end of the cluster.

If ergot fails, methysergide (Deseril, Sansert) 1–2 mg three times a day is given and is effective in 70 to 80% of cases. This is a powerful 5-HT antagonist, but in contrast to pizotifen it has no antihistaminic action. A semisynthetic ergot alkaloid, it is a vasoconstrictor pro-drug metabolized to methylergometrine. Prolonged use, that is for more than 4 months, is dangerous, and as with ergotamine the course of treatment requires close hospital supervision. Retroperitoneal, pleural and mediastinal fibrosis are uncommon but serious complications of excessive medication. They usually but not always regress when treatment is stopped. Angina, claudication and vascular occlusion occasionally complicate therapy and patients must be warned of all these possible side effects and, at their onset, told to stop the drug. In refractory cases, a combination of ergot and methysergide may be effective, but should be supervised in hospital.

Short courses of prednisolone 30–60 mg/day are often effective in controlling attacks or in abbreviating an otherwise intransigent cluster, but long-term treatment should be avoided if possible because of toxicity. Aggravation of coincident peptic ulcer is a risk. Relapses are likely if the dose is reduced to 10–20 mg/day.

Inhalation of portable oxygen 8 l/min at 100% concentration for 10–15 minutes may afford good

relief within 10 minutes in individual attacks. But it is cumbersome and a fire hazard.

Lithium is of limited value in episodic cluster headache, affording relief in 50 to 60% of patients. The relief may be incomplete, and the delay in establishing a steady state necessitates other faster-acting treatment of individual attacks, such as ergotamine or oxygen. But lithium may be invaluable in some victims of the chronic variant, used in doses of 200 mg 3–5 times/day. Dosage has to be monitored by serum lithium measurements to avoid toxicity, although good therapeutic results may occur with levels below the standard 'therapeutic range'. The mechanism of action is unknown, but claims are made for an effect on biological circadian rhythms which may include the rapid eye movement (REM) phase of sleep which is related to the timing of some cluster attacks. Side effects include tremor, polyuria, thirst, diarrhoea and thyroid dysfunction. Care must be taken if diuretics are administered for other reasons.

Other measures, taken with inconstant success, included propranolol, pizotifen and nifedipine. Verapamil is found effective by some workers. Ekbom has reported a recent trial of sumitriptan 6 mg by subcutaneous injection and found attacks aborted within 15 minutes in 74% of patients. In rare instances division of the greater superficial petrosal nerve or radiofrequency lesions of the trigeminal ganglion are required.

Conclusion

Future research will probably be directed at exploring why there is such striking male predominance, and why there is a disturbance of the biological clocks which determine the curious pattern of clusters and their crepuscular habits. Investigations will pursue hormonal factors, neuropeptides which mediate pain and the mechanisms underlying the curiously unilateral sympathetic/parasympathetic disorder. In the interim, assiduous attention to detail will afford satisfactory symptomatic control in most cluster headache victims.

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