The Spectrum of Disease: A Case Report of Epicrania Fugax Preceded by Reverse Ascending Cluster Headache with Successful Response to Fremanezumab

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🤔 Background and Objective:

Epicrania fugax (EF) is characterized by brief electrical linear trajectory pains in different nerve distributions, which 30% of the patients experience autonomic features at the end of the pain **(summarized criteria in table 1)**. In contrast, **cluster headache (CH)** is characterized by severe, strictly unilateral pains in the orbital, supraorbital, or temporal area, lasting from 30 minutes to 3 hours. The pain is associated with restlessness and ipsilateral autonomic features. A variant of CH that starts as mild-to-moderate pain at the occipital region and gradually moves towards the orbital area is called the **ascending CH** reported by Senna-Candel et al. **Ascending CH** fulfills the criteria of CH **(summarized in table 2)** but has a pain character of trajectory pain in different nerve distributions like EF. We report a patient who was diagnosed with reverse ascending CH followed by EF and much improved with anti-calcitonin gene-related peptide (CGRP) therapy.

😇 Result:

A 39-year-old female patient with a 12-year history of high-frequency episodic migraine with visual aura sought consultation at a neurology clinic due to the emergence of a new type of headache over the last 4 years. These new headache attacks always occurred in the late afternoon around 3 P.M., and each episode started with moderately severe stabbing pain (intensity 6/10 on a visual analog scale (VAS)) at the left eyebrow. Then, the pain moved backward along a linear trajectory, reaching the ipsilateral occipital area in 10 minutes. During the peak of headache, the pain at her eyebrow became sharp and excruciating (intensity 10/10 on VAS), accompanied by tearing, conjunctival injection, ptosis of the left eye, and restlessness. Without treatment, the pain lasted from 30 minutes to 3 hours. The patient sought treatment where she was diagnosed with CH and was treated by a combination of 400 mg/day of gabapentin, 25 mg/day of nortriptyline, 480 mg/day verapamil, sumatriptan, naproxen, and paracetamol/tramadol as needed. Despite the effective dose of treatment, the headaches persisted with the same character. However, they became just a few seconds in duration and had a higher frequency, occurring up to 50 times on certain days. As a result, the patient decided to seek further evaluation at our hospital. Her headache medications were then adjusted to 1200 mg/day of gabapentin, 30 mg/day of propranolol, 40 mg/day of nortriptyline. Other past medical illnesses included nonactive Grave's disease which was treated with 7.5 mg/day of methimazole. Physical and neurological examinations showed unremarkable findings. Brain magnetic resonance imaging was unremarkable.

She was diagnosed with EF due to the short duration and linear trajectory of the headache, which started at the left orbital region and projected towards the occipital region, as defined by ICHD-3. Additionally, the pain from 4 years ago was nearly similar to ascending CH but showed a backward projection, which we defined as "reverse ascending CH". Due to more frequent and disabling episodic migraines, she was administered a 225 mg subcutaneous injection of fremanezumab for 3 months. Three months after the administration of fremanezumab, she reported the resolution of the symptom of EF and ascending CH as well as less frequent episodes of migraines.

👨🏻‍⚕️ Methods:

We report a patient who was diagnosed with EF preceded by trajectory backward pain projection. We proposed the opposite pain projection of ascending CH as "reverse ascending CH". Informed consent was obtained from patient.

Figure 1: The conceptualized spectrum of disease.

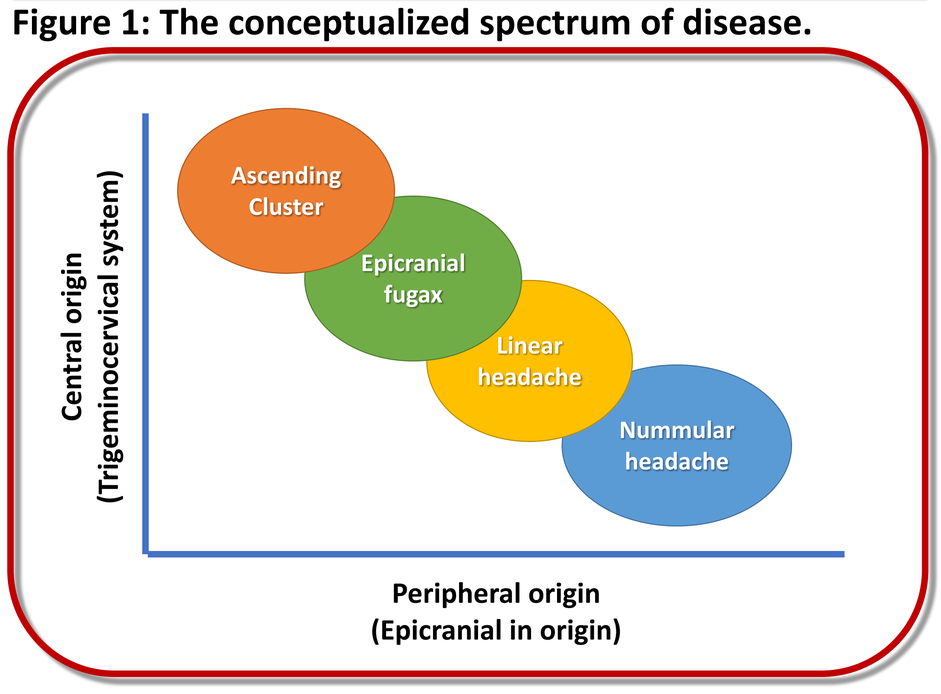

Table 1 Dianostic criteria of epicranial fugax (ICHD-3) – A4.11

1.Recurrent stabbing head pain attacks lasting 1-10 seconds and fulfilling criterion B
2.Pain moving with a linear or zig-zag trajectory across the surface of one hemicranium, commencing and terminating in the distributions of different nerves
3.Not better accounted for by another ICHD-3 diagnosis[1].

Table 2 Dianostic criteria of cluster headache (ICHD-3) – A3.1

1.At least five attacks fulfilling criteria B-D
2.Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)[1]
3.Either or both of the following:
  1. at least one of the following symptoms or signs, ipsilateral to the headache:
    1.– conjunctival injection and/or lacrimation
    2.– nasal congestion and/or rhinorrhoea
    3.– eyelid oedema
    4.– forehead and facial sweating
    5.– miosis and/or ptosis
  2. a sense of restlessness or agitation
4.Occurring with a frequency between one every other day and 8 per day[2]
5.Not better accounted for by another ICHD-3 diagnosis.

🤩 Conclusion

EF and ascending CH may not be distinct entities but rather a spectrum of disease that involves peripheral mechanisms such as trigeminal and cervical afferent fibers, as well as central mechanisms such as the trigeminocervical complex, trigeminal-parasympathetic pathway, and hypothalamus. Although the EF pathogenesis remains unclear, the possible pathogenic mechanism was explained by the ascending pain pathway of the peripheral pain generator from the pericranial nerve, in which CGRP plays role in the pain pathway. EF and ascending CH may play a dominant role in peripheral mechanisms, while migraine may play a dominant role in central mechanisms. The proposed spectrum of disease was summarized in **Figure 1**. The anti-CGRP terminating pain transmission in the peripheral pathway can be used in treating the refractory migraine and reverse ascending CH like this case. Further study of the correlation between EF and ascending CH is needed.

Reference:

1. Serna-Candel C, Cuadrado-Pérez ML, Guerrero-Peral ÁL, García-Ptacek S, Porta-Etessam J. Ascending cluster headache: a description of three cases and a review of the literature. *Rev Neurol*. 2011;52(7):412-416.
2. Jin P, Wang Y. Atypical cluster and migraine headache starting with a reverse epicrania fugax. Pain Med. 2013;14(5):765-766.

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