Caso Clinico

Alessandra Del Bene

SOC Neurologia

Ospedale San Jacopo Pistoia

Azienda USL Toscana centro

Servizio Sanitario della Toscana

Dichiarazione

Nessun conflitto di interessi

Dott.ssa Alessandra Del Bene

Caso Clinico - Anamnesi

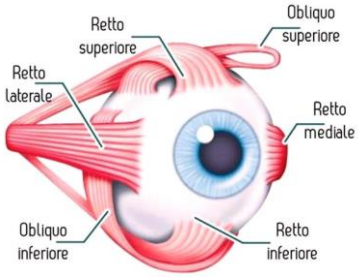
- Donna, 45 anni
- Familiarità per cefalea
- Sposata, 2 figlie, assume C.O., non fuma, non allergie
- Non patologie di rilievo in anamnesi patologica remota eccetto storia di cefalea:

- ✓ **dall'età di 6-7 anni crisi di emicrania senza aura**, successiva emicrania mestruale (crisi rare, solo tp sintomatica paracetamolo, FANS)
- ✓ **Dall'età di 20 anni** sono iniziate le **crisi di emicrania con aura episodica** (forse in relazione ad uso di C.O. estroprogestinici) con periodi di aumento frequenza degli attacchi (tp profilassi con flunarizina a cicli con vantaggio). Fattore scatenante (stress, emozioni)

  Nel **2005 episodio di cefalea occipitale, vomito, lipotimia e diplopia** (accertamenti di neuroimaging, EEG, laboratoristici, rachicentesi: ndn); nel 2007 e 2009 altri due episodi di cefalea con svenimento (ripetuti accertamenti neg)

Caso Clinico - Anamnesi

- **Da novembre 2021** la pz ha iniziato ad avere **crisi cefalalgiche associate a diplopia con paralisi VI nc** prevalentemente a sin, non altri sintomi associati (non nausea, vomito) di durata variabile (ore) a completa risoluzione.
- **Gennaio 2022 infezione da Sars-Cov2** con peggioramento della frequenza delle crisi cefalalgiche (ad aprile visita neurologica, terapia con pregabalin, accertamenti di neuroimaging, oculistici, laboratoristici ndr)
- **Settembre 2022** giunge in **PS** Ospedale San Jacopo Pistoia per insorgenza, mentre era alla guida dell'auto, con le figlie, di crisi di cefalea riferita dalla pz come **diversa dalle crisi abituali**: **cefalea parieto-occipitale di forte intensità, «esplosiva» associata a diplopia con strabismo convergente in OS da paralisi VI nc di sin, restante obiettività neurologica nella norma**



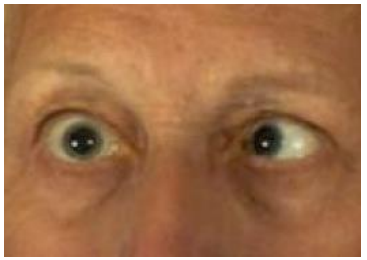
Cause di Oftalmoplegia dolorosa

Causes of painful ophthalmoplegia

(1) Trauma:
(2) Vascular:
Intracavernous carotid artery aneurysm
Posterior cerebral artery aneurysm
Carotid-cavernous fistula
Carotid-cavernous thrombosis
Posterior communicating artery aneurysm
Internal carotid artery dissection
(3) Neoplasm:
Primary intracranial tumour
Pituitary adenoma
Meningioma
Craniopharyngioma, others
Primary cranial tumour
Chordoma, others
Local metastases
Nasopharyngeal tumour
Squamous cell carcinoma
Distant metastases
Lymphoma
Multiple myeloma
Carcinomatous metastases

(4) Inflammation, infection:
Bacterial
Contiguous sinusitis
Mucocele (sphenoid sinus)
Periostitis
Abcess
Viral
Herpes zoster
Fungal
Mucormycosis, Actinomycosis
Spirochetal
Treponema pallidum
Mycobacterial
Mycobacterium tuberculosis
Others
Sarcoidosis
Granulomatosis with polyangiitis
Eosinophilic granuloma
Tolosa-Hunt syndrome
Orbital pseudotumor
(5) Miscellaneous:
Diabetic ophthalmoplegia
Ophthalmoplegic migraine / Recurrent painful ophthalmoplegic neuropathy
Giant cell arteritis

Cause di paralisi VI nervo cranico



Causes of sixth nerve palsy and associated features according to location

More common causes according to location	Common accompanying features*
Nuclear/fascicular lesions in the pons	
▪ Demyelinating ▪ Ischemic ▪ Neoplastic	▪ Horizontal gaze palsy; ipsilateral facial palsy; other brainstem signs including hemiparesis, hemisensory loss, and/or dysmetria
▪ Wernicke encephalopathy	▪ Encephalopathy, gait ataxia
Subarachnoid space lesions	
▪ Increased intracranial pressure from any cause including IIH	▪ Maybe bilateral, maybe associated with signs of increased intracranial pressure
▪ Microvascular sixth	▪ Isolated cranial nerve palsy, often with ipsilateral periorbital pain
▪ Aneurysm (causing nerve compression)	▪ Usually isolated cranial nerve palsy if unruptured aneurysm
▪ Meningeal inflammation or infiltration from infection, neoplasia, or inflammatory process	▪ Meningismus, other cranial mononeuropathies
▪ Low intracranial pressure	▪ Headache, nausea, and vomiting worse with upright posture
Petrous apex lesions	
▪ Neoplasm/tumor ▪ Infection or inflammatory (Gradenigo) ▪ Thrombosis of inferior petrosal sinus ▪ Traumatic, basilar skull, petrous apex fracture	▪ Facial pain (especially retro-orbital); fifth, seventh, eighth (deafness) cranial nerve involvement

IIH: idiopathic intracranial hypertension.

* Isolated sixth cranial nerve palsy can also occur in each of these locations.

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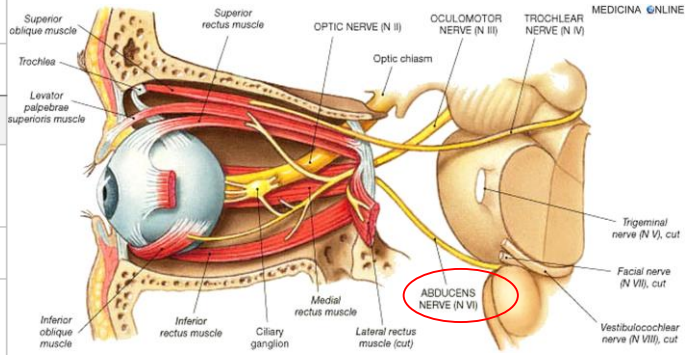
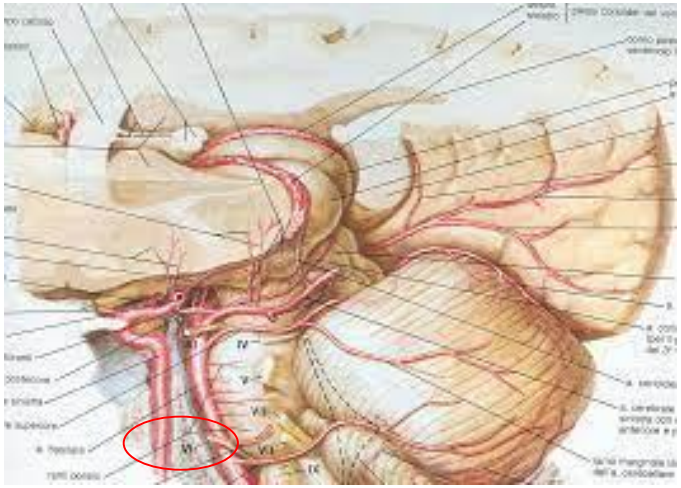


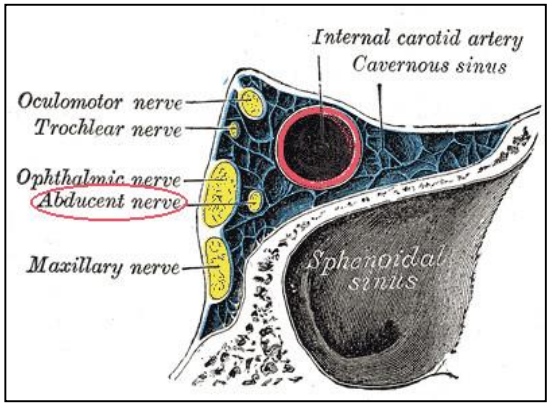


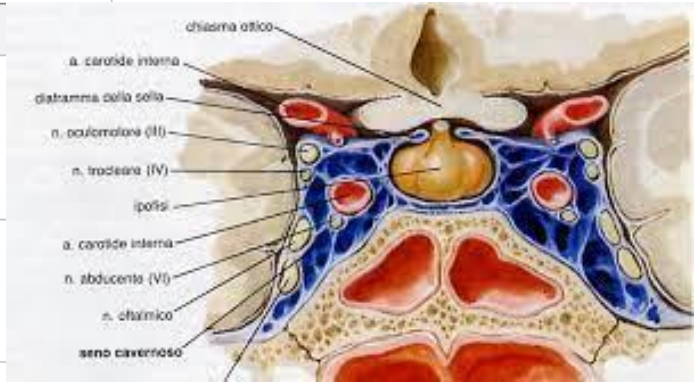
Causes of sixth nerve palsy and associated features according to location

More common causes according to location	Common accompanying features*
Cavernous sinus lesions	
▪ Cavernous sinus thrombosis ▪ Cavernous sinus fistula ▪ Neoplasm/tumor ▪ Pituitary adenoma ▪ Infections ▪ Inflammatory (including Tolosa-Hunt syndrome) ▪ Internal carotid artery aneurysm or dissection	▪ Impaired function of third, fourth, and fifth cranial nerves ▪ +/− ipsilateral Horner syndrome
Orbital lesions	
▪ Neoplastic ▪ Infectious ▪ Inflammatory (including orbital pseudotumor)	▪ Variably affected cranial nerve III, IV, V1 ▪ Proptosis, chemosis, compressive optic neuropathy

IIH: idiopathic intracranial hypertension.

* Isolated sixth cranial nerve palsy can also occur in each of these locations.





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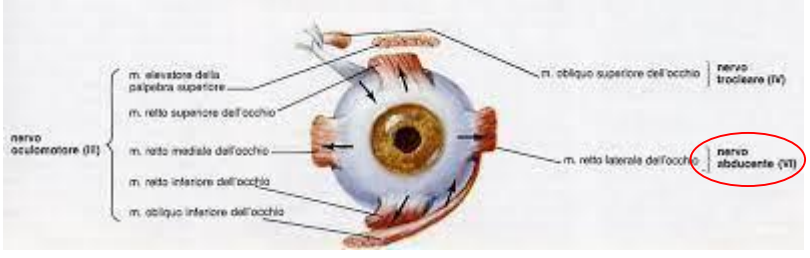
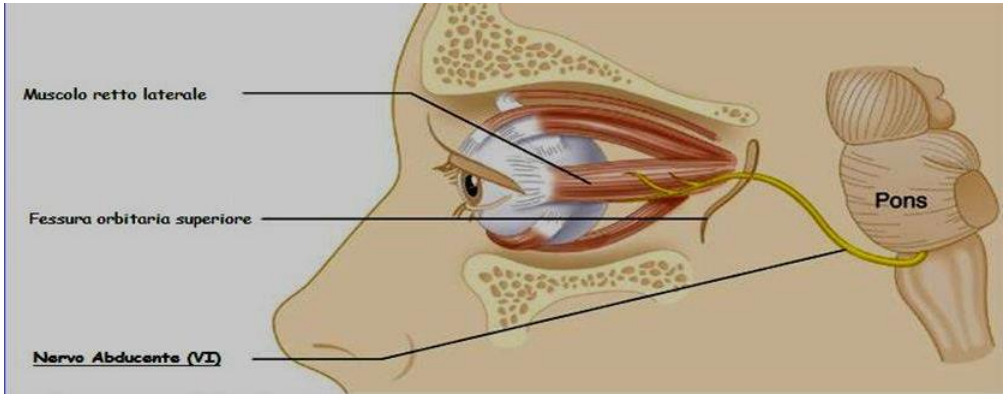
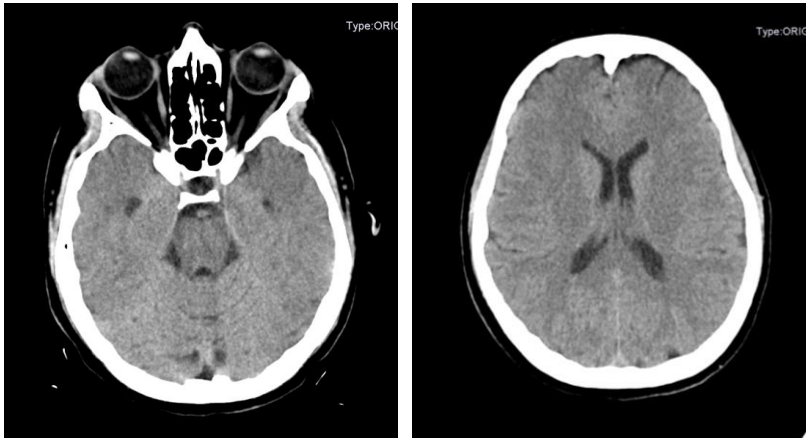




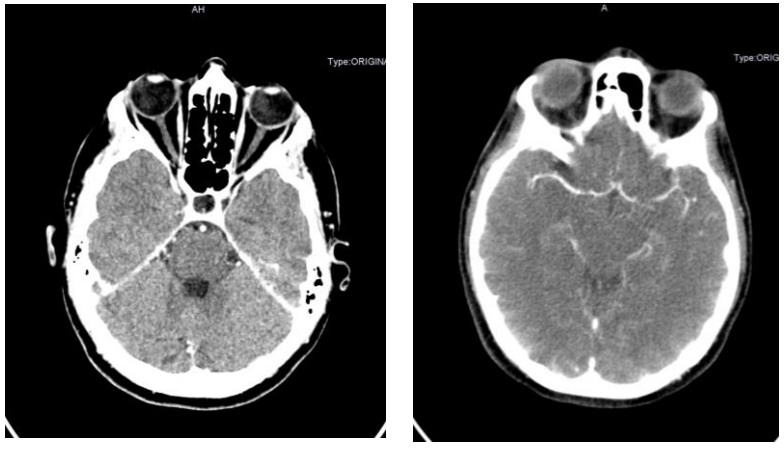
Caso Clinico – Gestione in PS

- Parametri vitali, PA , FC, Sat nella norma, non febbre
- Esami ematici, proteina C reattiva, fibrinogeno ndn
- Visita oculistica confermata diplopia, fondo e tono oculare nella norma, riflessi pupillari presenti.
- Imaging TC cranio + AngioTC nella norma

TC cranio encefalo

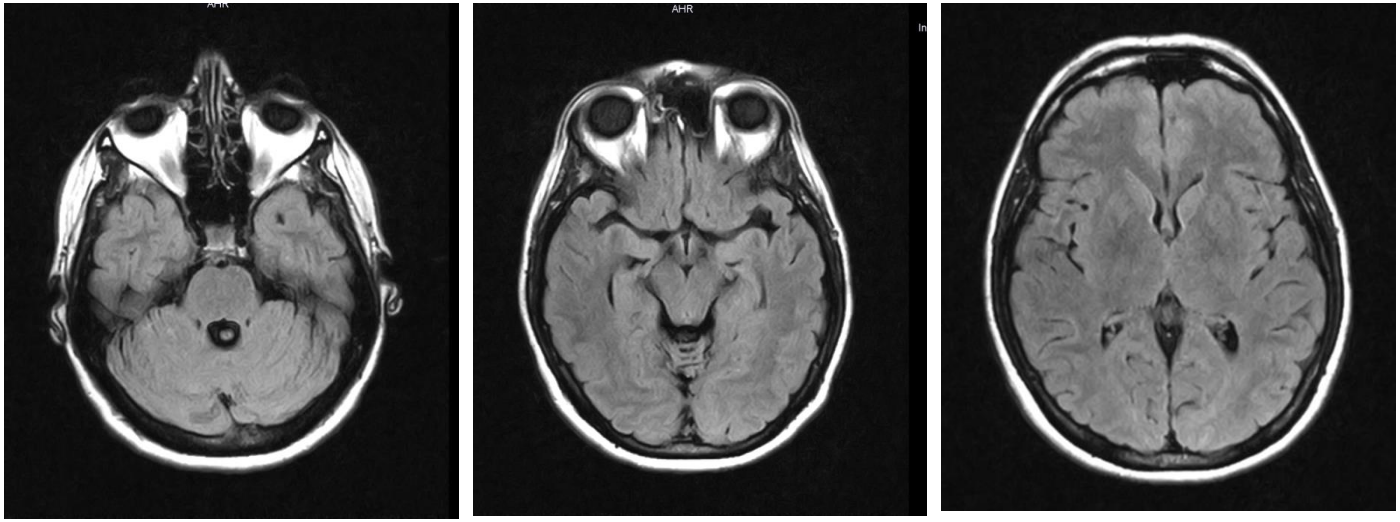


AngioTC vasi intracranici

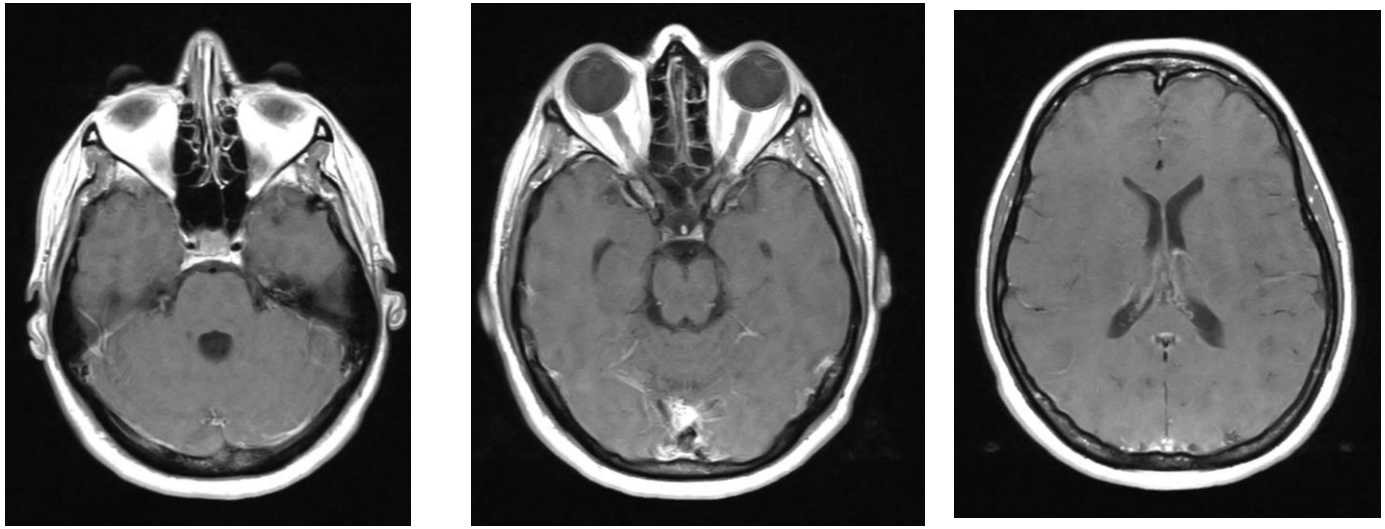


Ricovero in Neurologia

Caso Clinico – Work up diagnostico Imaging



RM encefalo+ orbite *seq. Flair*



RM encefalo *seq T1 con mdc*

Caso Clinico -Work up diagnostico

- Esami ematici (compresa funzionalità tiroidea, Hb glicata, VES, fattore reumatoide) screening TF e profilo AI: ndr
- Accertamenti cardiologici, ecoTSA negativi
- EEG nella norma

- **Terapia**: Desametasone 8 mg ev per 5 gg e successiva tp steroidea per os a scalare per dieci giorni + tp antiemicranica con flunarizina 5 mg/die alla dimissione per due mesi. Sospesa terapia con C.O.
- Alla dimissione programmata visita controllo a due mesi

- follow up a 2 mesi: riferito netto miglioramento delle crisi cefalalgiche

- In corso **follow up clinico e strumentale**

Diagnosi di dimissione

Neuropatia oftalmoplegica dolorosa ricorrente in paziente con emicrania con aura

International Classification of Headache Disorders

3rd edition

International Headache Society

ICHD 3. Cephalalgia 2018; 38: 1–211.

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2018, Vol. 38(1) 1–211

DOI: 10.1177/0333102417738202
journals.sagepub.com/home/cep
SAGE

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition

Part One: The Primary Headaches

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

Part Two: The Secondary Headaches

Introduction

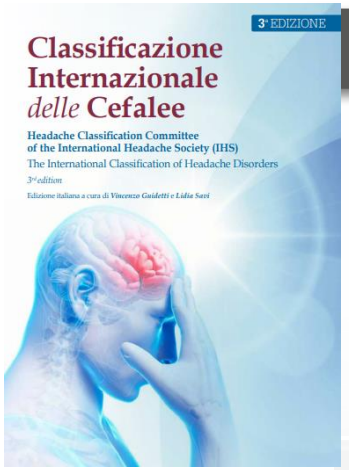
5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial and/or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder

Part Three: Painful Cranial Neuropathies, Other Facial Pain and Other Headaches

13. Painful lesions of the cranial nerves and other facial pain
14. Other headache disorders

Appendix

Definitions of terms



CAPITOLO 13

Neuropatie dolorose craniche e altri dolori faciali

13 NEUROPATIE DOLOROSE CRANICHE E ALTRI DOLORI FACIALI

13.1 Nevralgia trigeminale
- 13.1.1 Nevralgia trigeminale classica
  - 13.1.1.1 Nevralgia trigeminale classica, esclusivamente parossistica
  - 13.1.1.2 Nevralgia trigeminale classica con dolore faciale persistente
- 13.1.2 Neuropatia trigeminale dolorosa
  - 13.1.2.1 Neuropatia trigeminale dolorosa attribuita a Herpes zoster acuto
  - 13.1.2.2 Neuropatia trigeminale post-herpetica
  - 13.1.2.3 Neuropatia trigeminale post-traumatica
  - 13.1.2.4 Neuropatia trigeminale dolorosa attribuita a placca di Sclerosi Multipla (SM)
  - 13.1.2.5 Neuropatia trigeminale dolorosa attribuita a lesione occupante spazio
  - 13.1.2.6 Neuropatia trigeminale dolorosa attribuita ad altri disordini

13.2 Nevralgia glossofaringea

13.3 Nevralgia del nervo intermedio (nervo faciale)
- 13.3.1 Nevralgia del nervo intermedio classica
- 13.3.2 Neuropatia del nervo intermedio attribuita a Herpes zoster

13.4 Nevralgia occipitale

13.5 Neurite ottica

13.6 Cefalea attribuita a paralisi ischemica di un nervo oculomotore

13.7 Sindrome di Tolosa-Hunt

13.8 Sindrome paratrigeminale oculosimpatica (di Raeder)

13.9 Neuropatia oftalmoplegica dolorosa ricorrente

13.10 Sindrome della bocca urente (Burning mouth syndrome)

13.11 Dolore faciale idiopatico persistente (DFIP)

13.12 Dolore neuropatico centrale
- 13.12.1 Dolore neuropatico centrale attribuito a Sclerosi Multipla (SM)
- 13.12.2 Dolore centrale post-ictus

13.9 Neuropatia oftalmoplegica dolorosa ricorrente

Criteri diagnostici

A. Almeno due attacchi che soddisfino il criterio B

B. Cefalea unilaterale accompagnata da paralisi ipsilaterale di uno, due o tutti e tre i nervi oculomotori

C. Esclusione tramite opportune indagini di lesioni orbitarie, parasellari o in fossa cranica posteriore

D. Non meglio inquadrata da altra diagnosi ICHD-3

ICHD-3 *International Classification of Headache Disorders,* 2018

Review

Cephalalgia
An International Journal of Headache

International Headache Society

Proposed modified diagnostic criteria for recurrent painful ophthalmoplegic neuropathy: Five case reports and literature review

Cephalalgia
2020, Vol. 40(14) 1657–1670

DOI: 10.1177/0333102420944872
journals.sagepub.com/home/cep
SAGE

Yinglu Liu[1], Miao Wang[2], Xiangbing Bian[3], Enchao Qiu[4], Xun Han[1], Zhao Dong[1] and Shengyuan Yu[1]

Abstract

Background: Recurrent painful ophthalmoplegic neuropathy (RPON) is an uncommon disorder characterized by recurrent unilateral headache attacks associated with ipsilateral ophthalmoplegia. We intend to study the clinical picture in our case series along with the published literature to discuss the pathogenesis and propose modified diagnostic criteria for recurrent painful ophthalmoplegic neuropathy.

Methods: We reported five cases diagnosed as ophthalmoplegic migraine/RPON in our medical centers and reviewed the published literature related to RPON from the Pubmed database between 2000 and 2020. In one of these cases, a multiplanar reformation was performed to look at the aberrant cranial nerve.

Results: The mean onset age for RPON was 22.1 years, and the oculomotor nerve was the most commonly involved cranial nerve (53.9%) in 165 reviewed patients. In most patients, ophthalmoplegia started within 1 week of the headache attack (95.7%, 67/70). Additionally, 27.6% (40/145) of patients presented enhancement of the involved nerve(s) from MRI tests. Finally, 78 patients received corticosteroids, out of which 96.2% benefited from them.

Conclusion: This is the first time multiplanar reformation has been performed to reveal the distortion of the oculomotor nerve. Modified diagnostic criteria are proposed. We hope to expand the current knowledge and increase the detection of recurrent painful ophthalmoplegic neuropathy in the future.

Revisione letteratura anni 2000-2020
- 165 pz con diagnosi di neuropatia oftalmoplegica dolorosa ricorrente

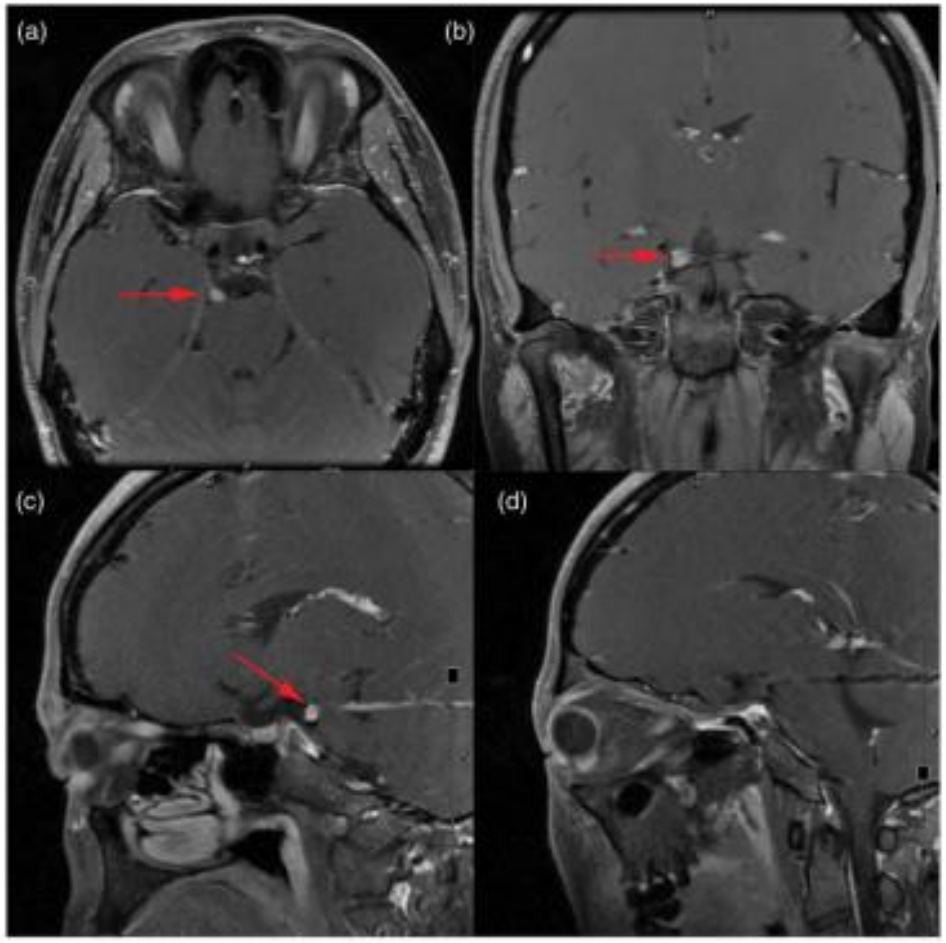
- Età media esordio 22 anni
- Sesso F nel 57% casi
- Nervo oculomotore più coinvolto, seguito dal nervo abducente e trocleare
- Alterazioni imaging 30% casi (soprattutto nei bambini)
- Risposta efficace a tp steroidea nel 96% pz

Neuropatia oftalmoplegica dolorosa ricorrente
Discussione

- ✓ Causa rara di oftalmoplegia dolorosa
- ✓ più frequente in età evolutiva
- ✓ Lieve prevalenza nel sesso femminile
- ✓ Incidenza annuale 0.7/1.000.000 abitanti
- ✓ Reperto imaging (RM encefalo con mdc) mostra ispessimento del nervo o potenziamento (*enhancement*)dopo gadolinio del nervo interessato. Risoluzione di tale reperto ad esame RM di follow up

Reperti di Neuroimaging utili nel processo diagnostico

Received enhanced MRI tests (n, %)	
Yes (n = 145, 87.9%)	
Abnormal	40 (27.6%, 40/145)
	<18 yrs 31 (63.3%, 31/49)#
	≥18 yrs 9 (34.6%, 9/26)
Normal	105 (72.4%, 105/145)
No (normal in regular MRI)	18 (10.9%)
NA	2 (1.2%)



- Alterazioni RM transitorie e reversibili
- Importanza di follow up di imaging a lungo termine

Figure 2. The enhanced MRI test of case 1. (a)–(c) T1-weighted post-gadolinium axial, coronal, and sagittal images show thickening and enhancement in the right oculomotor nerve (arrows); (d) normal sagittal images of the left oculomotor nerve.

Liu et al, *Cephalalgia,* 2020

Cureus

Open Access Case Report

DOI: 10.7759/cureus.25297

Recurrent Painful Ophthalmoplegic Neuropathy in an Adult Patient: A Case Report With Literature Review

Review began 05/10/2022
Review ended 05/21/2022
Published 05/24/2022

Shehbaz M. Ansari [1], Sumeet G. Dua [1], Mustafa Mafraji [1]

1. Department of Diagnostic Radiology and Nuclear Medicine, Rush University Medical Center, Chicago, USA

Corresponding author: Shehbaz M. Ansari, dr.shehbazansari@gmail.com

Abstract

Recurrent painful ophthalmoplegic neuropathy (RPON), previously known as ophthalmoplegic migraine, is a rare disease that predominantly affects children. Recurrent episodes of ocular cranial nerve paresis with ipsilateral headache characterize this disorder. Diagnosis is mainly clinical with imaging being used as an adjunct. The pathophysiology of the disease is unknown. We present here a case of RPON in a 50-year-old female presenting with multiple episodes of headache and diplopia with associated transient thickening and enhancement of the ipsilateral oculomotor nerve on magnetic resonance imaging (MRI).

Donna, 50 anni
Episodi ricorrenti di cefalea e diplopia.
Paralisi III nc sin
Transitorio *enhancement* del III nc sin ad esame RM con mdc.

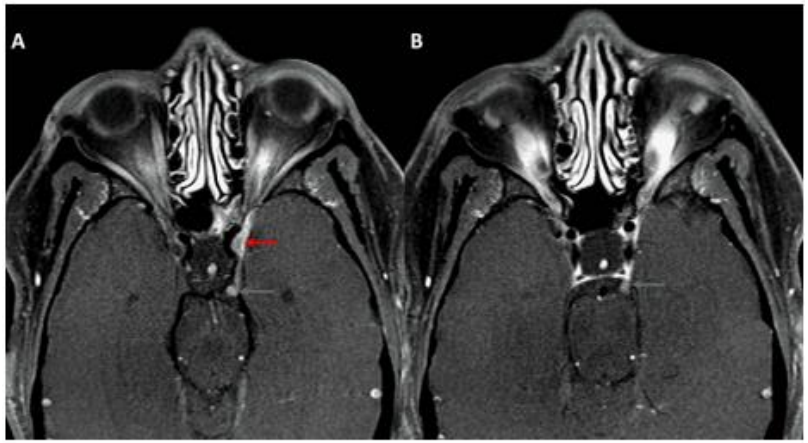


FIGURE 1: Postcontrast axial T1-weighted images (T1WI) showing nodular thickening in the region of the cavernous (red arrow in A) and cisternal segment (green arrows in A and B) of the left oculomotor nerve

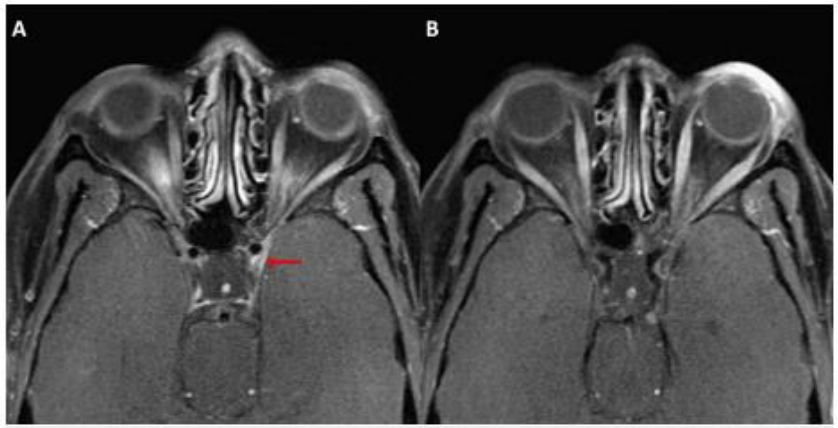


FIGURE 3: MRI orbit obtained four months later revealed a marked reduction in the thickening of the cavernous segment of the left oculomotor nerve (red arrow in A) and mild reduction in the cisternal segment (green arrow in B).

Neuropatia oftalmoplegica dolorosa ricorrente Discussione

- ✓ Prima identificata con il termine di emicrania oftalmoplegica coniato da Charcot nel 1890. Nel corso degli anni, sulla base dei casi descritti, riclassificata da variante emicranica (ICHD-1, 1988) a nevralgia cranica e neuropatia oftalmoplegica dolorosa ricorrente (ICHD-3, versione beta, 2013)

- ✓ Patogenesi poco conosciuta → ipotesi processo infiammatorio demielinizzante ricorrente

- ✓ Disturbo complesso con caratteristiche di neuropatia infiammatoria e non chiara associazione con l'emicrania→ dibattito tuttora in corso

COMMENTARY

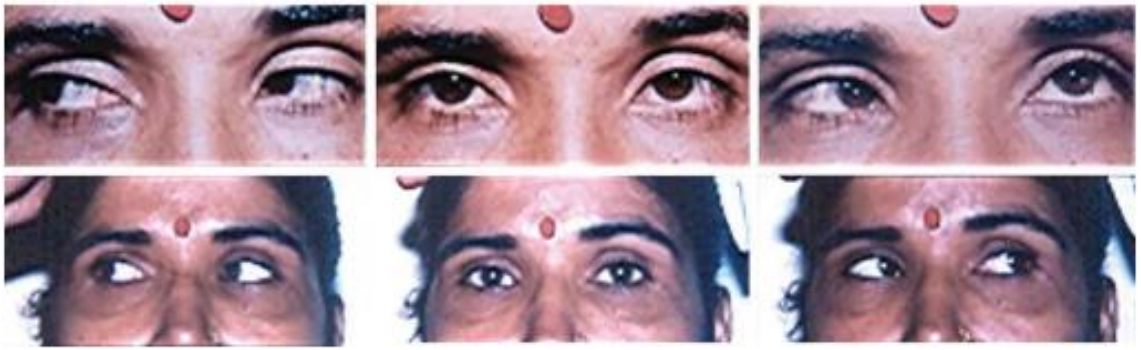
Are some ophthalmoplegias migrainous in origin?

Vivek Lal, DM, and Louis Caplan, MD

Neurology: Clinical Practice June 2019 vol. 9 no. 3 256-262 doi:10.1212/CPJ.0000000000000653

Correspondence
Dr. Lal
vivekl44@yahoo.com

Figure 1 Sixth cranial nerve palsy in ophthalmoplegic migraine

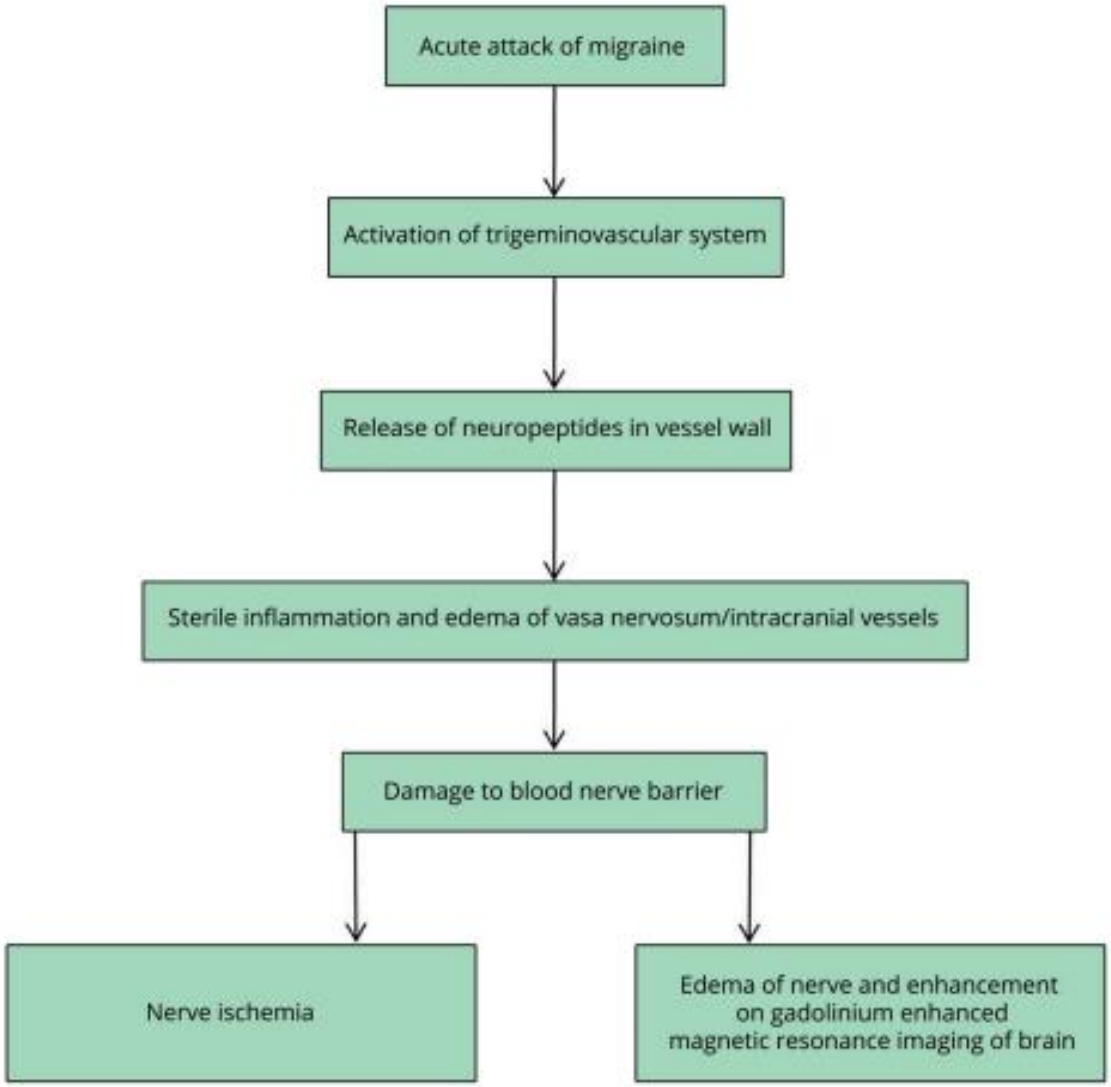


Sixth cranial nerve palsy in a 38 year old lady with ophthalmoplegic migraine. Note palsy of left lateral rectus (upper panel) during the attack and complete recovery (lower panel) after 10 weeks with antimigraine prophylaxis alone.

Donna, 38 anni. Familiarità per cefalea. Storia precedente di emicrania senza aura. Crisi con cefalea con dolore emicranico con oftalmoplegia (paralisi VI nc di sin).
RM encefalo con mdc: ndn.
Tp profilassi antiemicranica con significativo miglioramento

Lal and Caplan, *Neurology Clinical Practice*, 2019

Figure 3 Pathogenesis of nerve damage in ophthalmoplegic migraine



Proposed mechanism for palsies and enhancement of ocular motor nerves on magnetic resonance imaging in ophthalmoplegic migraine (adapted and modified from Lal et al.[18]).

Lal and Caplan, *Neurology Clinical Practice*, 2019

J Neuroophthalmol. 2022 Oct 18. doi: 10.1097/WNO.0000000000001695. Online ahead of print.

Serum Calcitonin Gene-Related Peptide Is Elevated in Patients With Migraine and Ophthalmoplegia

Aastha Takkar [1], K V Anil Kumar, Deeksha Katoch, Paramjeet Singh, Ranjana Minz, Shashi Anand, Soundappan Kathirvel, K Ravishankar, Vivek Lal, Louis R Caplan

Abstract

Background: There is ongoing debate about whether the oculomotor (III), trochlear (IV), or abducens (VI) nerve paresis in patients with migraine is directly attributable to migraine (ophthalmoplegic migraine [OM]) or is due to an inflammatory neuropathy (recurrent painful ophthalmoplegic neuropathy [RPON]). As migraine is associated with elevated serum calcitonin gene-related peptide (CGRP) levels, we studied serum CGRP levels among patients with OM/RPON to determine whether they are elevated during and between attacks. This is the first study assessing CGRP levels in the serum of patients with OM/RPON.

Methods: The aim of this case-control study was to assess serum CGRP levels in patients with ophthalmoplegia and a headache consistent with migraine according to ICHD-3 criteria. Serum CGRP levels were measured during the ictal and interictal phases in 15 patients with OM/RPON and compared with age-matched and sex-matched controls without migraine (12 patients).

Results: The median serum CGRP levels were significantly elevated (P = 0.021) during the ictal phase (37.2 [36.4, 43.6] ng/L) compared with controls (32.5 [30.1, 37.3] ng/L). Serum CGRP levels during the attack correlated with the total duration of ophthalmoplegia. A CGRP level of 35.5 ng/L in the ictal phase of the attack had a sensitivity of 86.7% and specificity of 75.0% in diagnosing a patient with OM/RPON.

Conclusion: Elevated serum CGRP levels during the ictal phase of OM/RPON favor migraine as the underlying cause of episodic headache with ophthalmoplegia.

Neuropatia oftalmoplegica dolorosa ricorrente
Conclusioni

- ✓ Prognosi buona per i singoli episodi, attacchi ripetuti possono portare ad un danno permanente del nervo
- ✓ Dati osservazionali a favore di trattamento steroideo + terapia di profilassi antiemicranica
- ✓ Migliore conoscenza sulla patogenesi necessaria per identificare il trattamento più adeguato
- ✓ Trattamento precoce di una entità clinica disabilitante
- ✓ Dati in letteratura sono limitati (case reports, piccole serie di casi)

Grazie per l’attenzione