Natural History of Isolated Microvascular CN III, IV and VI Pareses

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Financial Disclosure

No financial conflicts of interest

Case Presentation

62 year-old male with hypertension and hyperlipidemia presents with acute onset of an isolated left cranial nerve VI paresis and left retrobulbar pain

Case Presentation

- What initial diagnostic workup would you recommend?
- Is associated pain atypical? Does it change management?
- What would you advise patient in terms of expected recovery?
- What is the risk of recurrence? What workup is recommended if recurrence occurs?

Workup for Acute Isolated Ocular Motor Cranial Neuropathies in Age ≥ 50

- Controversial- immediate neuroimaging versus conventional diagnostic thresholding
- Thresholding uses pretest likelihood of disease to determine if diagnostic testing warranted

Red Flags- Neuroimaging Required

- Age < 50
- History of cancer
- Progression beyond 10 days
- Multiple cranial neuropathies
- Associated facial numbness or other neurologic signs
- Pupil-involving CN III paresis or non-pupil involving partial CN III paresis (need urgent MRA or CTA to rule out aneurysm)

Objectives

1. Review proposed pathophysiology
2. Understand risk factors
3. Review natural history
4. Consider an appropriate strategy for neuroimaging

Proposed Pathophysiology

Autopsy studies (microvascular CN III paresis) show:

- No vascular occlusion
- Focal myelin loss and fragmentation of nerve sheath in subarachnoid or intracavernous portion of nerve
- Preservation of underlying axons
- Vasa nevorum showed arterial hyalinization consistent with chronic vascular change
- Subsequent remyelination

Risk Factors

- Often presumptive clinical diagnosis made in absence of any symptoms/ signs suggestive of alternate diagnosis in patient in vasculopathic age group
- Few prospective studies assessing association of specific vascular risk factors

Risk Factors for Ischemic Ocular Motor Nerve Palsies

(Arch Ophthalmol. 1994;112:961-966)

Daniel M. Jacobson, MD; Terrence D. McCanna, MD; Peter M. Layde, MD, MSc

Retrospective case-control study

- 65 case patients ≥ age 50. Controls matched for gender and age
- Case patients underwent following workup: BP, labs: Hct, glucose, glucose tolerance test, Hgb A1c if known diabetic, cholesterol, EKG
- If no DM: AChR aby, CBC, ESR, SPEP, Lyme, syphilis, ANA. CXR and edrophonium test

Risk Factors for Ischemic Ocular Motor Nerve Palsies

(Arch Ophthalmol. 1994;112:961-966)

Daniel M. Jacobson, MD; Terrence D. McCanna, MD; Peter M. Layde, MD, MSc

Possible risk factors analyzed

- Diabetes
- Hypertension
- CAD
- CHF
- Left ventricular hypertrophy (LVH)
- Adiposity
- Tobacco use
- Family history of stroke or myocardial infarct
- Hematocrit
- Prior ocular motor nerve palsy

Table 1. Entry Criteria for Patients With Ischemic Ocular Motor Nerve Palsies

Inclusion criteria
- Age at least 50 y
- Evaluated within 2 wk of onset of symptoms
- No other neurological symptoms or signs at initial and all subsequent follow-up evaluations
- Negative forced duction testing (for third and sixth nerve palsies)
- Same pattern of ophthalmoplegia during follow-up
- Spontaneous complete recovery within 4 mo

Exclusion criteria
- History of childhood strabismus
- For third nerve palsies, pupil involvement (defined if pupil in affected eye was at least 0.4 mm larger than fellow pupil in room light and if degree of anisocoria diminished in darkness), or signs of aberrant regeneration
- For fourth nerve palsies, old head tilt observed by inspection of old photographs, large vertical fusion amplitudes, evidence of ambliyopia
- Head trauma within 3 mo of onset of symptoms
- Clinical features of Graves' ophthalmopathy
- External or orbital signs, such as exophthalmos, chemosis, hyperemia, soft tissue edema, arterialization, bruit
- Established or suspected multiple sclerosis
- Prior central nervous system disorder, except ocular motor or facial nerve palsy or stroke
- Laboratory or clinical features suggestive of Lyme disease, giant cell arteritis, myasthenia gravis, syphilis, or systemic vasculitis
- A patient with a known or suspected systemic malignant neoplasm who did not undergo a neuroimaging study that excluded a compressive lesion

Inclusion criteria
Age ≥ 50
Seen within 2 weeks of onset
Recovery within 4 months

Exclusion criteria
Head trauma within 3 months of onset
Pupil-involving CN III paresis
Signs of TED
Suspected multiple sclerosis
Suspected stroke
Suspected malignancy

Jacobson D et al. Risk factors for ischemic ocular motor nerve palsies. Arch Ophthalmol. 1994

Table 2. Characteristics and Distribution of 65 Patients With Ischemic Ocular Motor Nerve Palsies

Characteristic	No. (%) of Cases
Age, y	
50-59	10 (15.4)
60-69	22 (33.8)
70-79	25 (38.5)
80-89	6 (9.2)
90-99	2 (3.1)
Sex	
F	23 (35.4)
M	42 (64.6)
Nerve affected	
Third	18 (27.7)
Fourth	21 (32.3)
Sixth	26 (40.0)
Laterality of affected nerve	
R	35 (53.8)
L	30 (46.2)
Painful	
Yes	35 (53.8)
No	30 (46.2)
Progression*	
Yes	12 (27.3)
No	32 (72.7)

*Refers to those patients with oculomotor or abducens nerve palsies only.

- CN VI most frequently affected
- > 50% patients reported associated pain

Jacobson D et al. Risk factors for ischemic ocular motor nerve palsies. Arch Ophthalmol. 1994

Table 3. Distribution of Potential Risk Factors for Ischemic Ocular Motor Nerve Palsy in 65 Case Patients and Controls With Unadjusted Odds Ratio

Risk Factor	No. (%) Positive: Case Patients	Controls	Unadjusted Odds Ratio* (95% Confidence Interval)
Previously diagnosed diabetes	27 (41.5)	7 (10.8)	5.88 (2.17-15.93)
Insulin-dependent diabetes	14 (21.5)	1 (1.5)	14.27 (1.87-108.8)
Hypertension	43 (66.2)	36 (55.4)	1.72 (0.79-3.75)
Previously diagnosed hypertension	32 (49.2)	33 (50.8)	0.94 (0.47-1.89)
Hypercholesterolemia	30 (46.2)	29 (44.6)	1.06 (0.54-2.11)
Coronary artery disease	21 (32.3)	15 (23.1)	1.57 (0.73-3.38)
Congestive heart failure	4 (6.2)	1 (1.5)	4.16 (0.45-38.04)
Left ventricular hypertrophy	15 (23.1)	6 (9.2)	2.93 (1.03-8.30)
Tobacco use	10 (15.4)	6 (9.2)	1.70 (0.61-4.75)
Family history of stroke	0 (0.0)	1 (1.5)	0.00
Family history of myocardial infarction	6 (9.2)	9 (13.8)	0.65 (0.23-1.88)
Prior ocular motor nerve palsy	10 (15.4)	2 (3.1)	5.74 (1.20-27.52)
Prior stroke	3 (4.6)	4 (6.2)	0.63 (0.09-4.27)
Cervical bruit	1 (1.5)	3 (4.6)	0.33 (0.03-3.20)

*Odds ratio estimate from conditional logistic regression controlling only for the matching factors of sex and exact year of age.

3 independent risk factors:
1. DM
2. LVH
3. Elevated Hct

After controlling for these risk factors, prior ocular motor palsy was no longer statistically associated

Jacobson D et al. Risk factors for ischemic ocular motor nerve palsies. Arch Ophthalmol. 1994

Table 4. Distribution of Continuously Measured Risk Factors and Other Characteristics in 65 Case Patients With Ischemic Ocular Motor Nerve Palsy and in Controls*

Factor	Case Patients: Mean	SD	No.	Controls: Mean	SD	No.	P
Hemoglobin A_{1c}, %†	9.09	1.54	18	6.98	2.02	6	.0135‡
Cholesterol, mmol/L (mg/dL)	5.85 (226.1)	1.04 (40.3)	59	5.56 (215.1)	1.06 (41.0)	65	.1170§
Hematocrit	0.44	0.032	60	0.42	0.032	65	.0002§
Quetelet's index, g/cm²	2.95	0.50	65	2.77	0.523	65	.0930§
Duration of diabetes, y	13.1	10.29	26	8.6	7.37	7	.2844‡

*No. indicates number of case patients or controls who had this variable analyzed.
†Refers to only those case patients and controls with previously established diabetes.
‡Derived from unpaired Student's t test.
§Derived from paired Student's t test.

Poor diabetic control predisposes to ocular motor cranial nerve paresis

Jacobson D et al. Risk factors for ischemic ocular motor nerve palsies. Arch Ophthalmol. 1994

Table 5. Logistic Regression Model of Independent Risk Factors for Ischemic Ocular Motor Nerve Palsy

Risk Factor	Odds Ratio (95% Confidence Interval)
Previously diagnosed diabetes	5.75 (1.68-19.70)
Left ventricular hypertrophy	5.20 (1.30-20.82)
Hematocrit (per percentage change)	1.35 (1.13-1.61)

*Odds ratio estimate from conditional logistic regression model, including the three risk factors noted and controlling for matching by sex and exact year of age.

Percentage point ↑ in Hct associated 35% ↑ risk of ocular motor nerve paresis
Viscosity is inversely proportional to rate of microvascular blood flow

Jacobson D et al. Risk factors for ischemic ocular motor nerve palsies. Arch Ophthalmol. 1994

Diabetes and Hypertension in Isolated Sixth Nerve Palsy

A Population-Based Study Ophthalmology 2005;112:760-763

Sanjay V. Patel, BMBS,[1] Jonathan M. Holmes, BM, BCh,[1] David O. Hodge, MS,[2] James P. Burke, PhD[2]

Retrospective case-control study (1978-1992)

- 76 case patients with isolated CN VI paresis. Controls matched for gender and age
- Cases were defined as non-traumatic, neurologically isolated CN VI paresis without underlying systemic disease other than DM or HTN
- Compared prevalence of pre-existing DM and HTN in patients with isolated CN VI paresis versus controls

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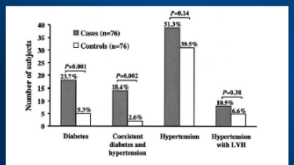

Figure 1. The number of cases of sixth nerve palsy and the number of controls who met the strict criteria for the presence of diabetes (with or without hypertension), coexistent diabetes and hypertension, hypertension (with or without diabetes), and hypertension with left ventricular hypertrophy (LVH).

- DM more frequent in cases (6x odds ratio)
- Concurrent DM and HTN more frequent in cases (8x odds ratio)
- HTN alone or LVH not associated with statistically significant increased odds-ratio

Risk Factors

Vascular risk factors

- Diabetes
- Hypertension
- Hypercholesterolemia
- Coronary artery disease

Each significantly associated with microvascular cranial neuropathy in patients ≥ age 50 (RR 2.13, p= 0.0004)

Chou et al. Acute ocular motor mononeuropathies: prospective study of the roles of neuroimaging and clinical assessment. Journal of the Neurological Sciences 2004

Risk Factors

Vascular risk factors

- Diabetes
- Hypertension
- Hypercholesterolemia
- Coronary artery disease
- Stroke
- Smoking

Each significantly associated with microvascular cranial neuropathy in patients ≥ age 50 (p= 0.003)

Tamhankar et al. Isolated third, fourth and sixth cranial nerve palsies from presumed microvascular versus other causes. Ophthalmology 2013.

Is Pain Atypical?

Pain in Ischemic Ocular Motor Cranial Nerve Palsies

Shawn C. Wilker, MD, Janet C. Rucker, MD, Nancy J. Newman, MD, Valerie Biousse, MD, and Robert L. Tomsak, MD, PhD *Br J Ophthalmol.* 2009 December ; 93(12): 1657–1659.

- Multicenter retrospective and prospective chart reviews of 87 patients who improved or fully resolved within 6 months
- Goal: Evaluate presence of pain in ischemic ocular motor cranial nerve pareses
- Average age 67 (range 42-91)
- 48 CN VI paresis, 39 CN III paresis, 5 CN IV paresis
- Brain MRI performed to exclude alternate diagnosis

Pain in microvascular ocular motor cranial nerve palsies.

MP events	Pain	No pain
All (n = 92)	57 (62%)	35 (38%)
CN VI (n = 48)	26 (54%)	22 (46%)
CN III (n = 39)	30 (77%)*	9 (23%)
CN IV (n = 5)	1 (20%)	4 (80%)
In diabetics (n = 36)	26 (72%)**	10 (28%)
In non-diabetics (n = 56)	31 (55%)	25 (45%)

Pain severity

	CN III	CN IV	CN VI
Mild	7 (33%)	0 (0%)	12 (63%)
Moderate	5 (24%)	1 (100%)	4 (21%)
Severe	9 (43%)	0 (0%)	3 (16%)

Abbreviations: MP = microvascular ocular motor cranial nerve palsies
CN VI = abducens nerve
CN III = oculomotor nerve
CN IV = trochlear nerve

* Pain in CN III palsies was significantly more common than in CN VI palsies (p-v =0.042)

** No statistically significant difference was found for the presence or absence of pain between diabetics and nondiabetics

Wilker et al. Pain in ischemic ocular motor cranial nerve palsies Br J Ophthalmol 2009

Pain in Ischemic Ocular Motor Cranial Nerve Palsies

Shawn C. Wilker, MD, Janet C. Rucker, MD, Nancy J. Newman, MD, Valerie Biousse, MD, and Robert L. Tomsak, MD, PhD *Br J Ophthalmol.* 2009 December ; 93(12): 1657–1659.

- Pain usually concurrent with diplopia but in 1/3 cases preceded diplopia by 6 days +/- 5 days
- Mild or moderate pain lasted on average 10 days
- Severe pain lasted on average 26 days
- No correlation between having diabetes and experiencing painful ischemic ocular motor cranial neuropathy

What is Prognosis for Recovery?

Prognosis

Microvascular CN III, IV and VI paresis

- Jacobsen et al. 65 cases- resolution after mean 8.8 weeks +/- 3.7 weeks (inclusion criteria limited to patients with complete resolution within 4 months)
- Wilker et al. 92 cases- improvement usually occurred within 2-3 months

Microvascular CN VI paresis

- Sanders et al. 59 cases of CN VI paresis- 86% complete resolution, 14% partial recovery) within 12 weeks

Clinical features and natural history of acquired third, fourth, and sixth cranial nerve palsy

U-C Park[1,2], S-J Kim[1,2], J-M Hwang[1,2,3] and YS Yu[1,2]

Eye (2008) 22, 691–696

www.nature.com/eye

- Retrospective review 206 cases of CN III, IV, VI paresis from 1998-2005 (64 patients- microvascular etiology)
- Goal: To determine clinical factors predictive of recovery
- Vascular etiology: 87% improved (complete and partial recovery), 62% resolved (average time to recovery 3.5 months)
- Initial smaller angle deviation only factor associated with complete recovery

What is Risk of Recurrence?

Long-term Prognosis in Patients With Vasculopathic Sixth Nerve Palsy

Am J Ophthalmol. 2002

SCOTT K. SANDERS, MD, AKI KAWASAKI, MD, AND VALERIE A. PURVIN, MD

- Observational case series, retrospective 1983-1996
- 59 patients, mean age 65 +/- 12 years
- Mean follow-up 6 years (range 2-13 years)
- Questionnaires to assess recurrent diplopia since last exam. Diagnosis made by direct exam, outside record review or patient report (87% response rate)
- All had spontaneous improvement (51 complete resolution, 8 partial recovery) within 12 weeks

TABLE 2. Relationship of Vasculopathic 6NP Resolution and Recurrence of Ocular Motor Nerve Mononeuropathies to Vascular Risk Factors

		Resolution			Recurrence		
Risk Factors	Totals n = 59 (%)	Complete (86%) n = 51 (%)	Incomplete (14%) n = 8 (%)	P	Yes (31%) n = 18 (%)	No (69%) n = 41 (%)	P
HTN*	42 (71)	37 (73)	5 (63)	0.68	14 (78)	28 (68)	0.55
DM*	32 (54)	30 (59)	2 (25)	0.13	11 (61)	21 (51)	0.78
HCLC*	28 (48)	24 (47)	4 (50)	1.0	10 (56)	18 (44)	0.41
TOB*	31 (53)	27 (53)	4 (50)	1.0	9 (50)	22 (54)	0.57
Male (%)*	32 (54)	29 (91)	3 (9)	0.45	11 (34)	21 (66)	0.89
Female (%)*	27 (46)	22 (81)	5 (19)		7 (26)	20 (74)	
Age (avg.)†	65.3	65.8	61.8	0.34	65.3	65.3	0.45
Treatable risk‡ factors per patient	2.25	2.31	1.88	0.30	2.56	2.20	0.91

DM = diabetes mellitus; HCLC = hypercholesterolemia and/or hyperlipidemia; HTN = hypertension; TOB = tobacco use.
*P values from chi square or the Fisher exact test.
†P values from the two-tailed Student *t* test.

- 31% recurrence
- No association between number of microvascular risk factors or specific factors (DM, HTN, hyperlipidemia, smoking, sex and age) and incomplete recovery or recurrence

Sanders S , Kawasaki A, Purvin V. Long-term prognosis in patients with vasculopathic sixth nerve palsy. Am J Ophthalmol. 2002

Workup for Recurrent CN VI Paresis?

Causes of isolated recurrent ipsilateral sixth nerve palsies in older adults: a case series and review of the literature

Jane W Chan[1,2]
Jeff Albretson[3]

Clinical Ophthalmology
23 February 2015

- Retrospective case series 1995-2005, 782 patients
- 7 cases of recurrent CN VI paresis age ≥ 50
- All were ipsilateral
- Neurologically isolated with exception of headache or periorbital pain (1st month of onset)
- Duration of initial diplopia 2 weeks- 3 months
- Interval between diplopia recurrence 5 months- 2 years

Causes of isolated recurrent ipsilateral sixth nerve palsies in older adults: a case series and review of the literature

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Table 1 Causes of isolated recurrent sixth nerve palsy over a 10-year period in a single clinic

Age, years	Sex	Causes of isolated recurrent sixth nerve palsy
52	M	Intracavernous carotid artery aneurysm
57	F	Recurrent painful ophthalmoplegic neuropathies (ophthalmoplegic migraine)
60	M	Microvascular disease (hypertension and diabetes)
62	M	Parasellar meningioma
71	M	Petrous apex meningioma
72	F	Metastatic melanoma in prepontine cistern cavernous sinus and sphenoid sinus
79	M	Peripontine meningioma

Notes: In a retrospective review of the medical records database over a 10-year period in a neuro-ophthalmology clinic in Reno, Nevada, USA, of 782 patients, seven consecutive patients ≥50 years of age were identified with a diagnosis of isolated recurrent sixth nerve palsies.

Only 1 recurrent CN VI paresis was ultimately attributed to a microvascular etiology

Causes of isolated recurrent ipsilateral sixth nerve palsies in older adults: a case series and review of the literature

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- 71% had a structural cause!
  - 57% (4/7) mass lesion in petrous apex or parasellar region
  - 14% (1/7) intracavernous ICA aneurysm
- 1/7 microvascular
- 1/7 recurrent painful ophthalmoplegic neuropathy
- High yield to neuroimaging for recurrent CN VI paresis

Should All Patients Have Neuroimaging?

Isolated Third, Fourth, and Sixth Cranial Nerve Palsies from Presumed Microvascular versus Other Causes

A Prospective Study

Ophthalmology 2013;120:2264-2269

Madhura A. Tamhankar, MD,[1] Valerie Biousse, MD,[2] Gui-Shuang Ying, MD, PhD,[3] Sasheeh Prasad, MD, PhD,[2] Prem S. Subramanian, MD, PhD,[4] Michael S. Lee, MD,[5] Eric Eggenberger, DO,[6] Heather E. Moss, MD, PhD,[7] Stacy Pineles, MD,[8] Jeffrey Bennett, MD, PhD,[9] Benjamin Osborne, MD,[10] Nicholas J. Volpe, MD,[11] Grant T. Liu, MD,[1] Beau B. Bruce, MD, MS,[1] Nancy J. Newman, MD,[1] Steven L. Galetta, MD,[1] Laura J. Balcer, MD, MSCE[1]

- Multicenter prospective observational case series
- 109 patients ≥ age 50 with acute isolated ocular motor nerve palsy (*isolated- may have orbital pain or headache)
- Seen within 30 days of onset
- Exclusions: Head trauma, prior strabismus, orbital disease, neurosurgical intervention or lumbar puncture, contraindication to MRI
- 95% re-examined at 8-12 weeks (6 telephone follow-up)

Isolated Third, Fourth, and Sixth Cranial Nerve Palsies from Presumed Microvascular versus Other Causes

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Study Patients

- Cranial nerve III paresis: 22 (18 partial, 4 complete pupil-sparing)
- Cranial nerve IV paresis: 25
- Cranial nerve VI paresis: 62
- All underwent MRI brain without and with gadolinium
- +/- ESR/CRP, AChR aby, TAB, LP

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Results

- 16.5% (18 patients) had a structural/ alternate cause
- Presence of ≥ 1 vascular risk factors significantly associated with microvascular etiology (p= 0.003)
- Vascular risk factors also present in 61% (11/18) with other causes

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- If CN III paresis were excluded, 4.7% (3/64) had a structural cause
  - Age 68 with multiple vasculopathic risk factors- isolated CN IV paresis due to dorsal midbrain infarct
  - Age 58 with HTN, hypercholesterolemia- isolated CN VI paresis due to B cell lymphoma infiltrating cavernous sinus
  - Age 53 without vascular risk factors- isolated CN VI paresis due to petroclival meningioma

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Conclusions

"A substantial proportion of patients had other causes including neoplasm, GCA, and brain stem infarction.

Brain MRI and laboratory workup have a role in the initial evaluation of older patients with isolated acute ocular motor nerve palsies regardless of whether vascular risk factors are present."

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Neuroimaging and Acute Ocular Motor Mononeuropathies

A Prospective Study Arch Ophthalmol 2011

Ann P. Murchison, MD, MPH; Molly E. Gilbert, MD; Peter J. Savino, MD

- 93 patients > age 50 with acute isolated cranial mononeuropathies (CN III, IV or VI)
- CN III paresis: 14, CN IV paresis: 27, CN VI paresis: 52
- All underwent MRI brain
- Number of MRI lesions and cost (Medicare 2010 dollars) recorded
- Total cost of neuroimaging $131,688 ($1416 per scan including professional fees)

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Neuroimaging and Acute Ocular Motor Mononeuropathies

A Prospective Study Arch Ophthalmol 2011

Ann P. Murchison, MD, MPH; Molly E. Gilbert, MD; Peter J. Savino, MD

Results

- 4 lesions identified (3 were incidental findings, 1 causative (pontine hemorrhage → CN VI palsy) but did not change management)
- 1.1% of scans showed a causative lesion

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Neuroimaging and Acute Ocular Motor Mononeuropathies

A Prospective Study

Arch Ophthalmol 2011

Ann P. Marchison, MD, MPH; Molly E. Gilbert, MD; Peter J. Savino, MD

Conclusions

- "Our study supports the traditional guidelines for imaging patients with acute, new onset mononeuropathies."

Table 3. Guidelines for Performing Magnetic Resonance Imaging in Patients With Cranial Nerve III, IV, and VI Palsies

Criterion
Aged <50 y
History of cancer of any type at any time
Other neurologic signs or symptoms
Pupil-involving or partial cranial nerve III palsy
No resolution 3 mo after initial visit

Case Presentation

- What initial diagnostic workup would you recommend?
  - Screening for DM (and Hgb A1c in known diabetics), HTN, hypercholesterolemia, elevated hematocrit
  - +/- screening for GCA, +/- neuroimaging
- Is associated pain atypical?
  - No, up to 2/3 patients present with transient ipsilateral brow/ retro-orbital pain
  - Pain is not more common in diabetics than non-diabetics

Case Presentation

- What would you advise patient in terms of expected recovery?
  - Majority have spontaneous resolution within 3-4 months
- What is the risk of recurrence? Appropriate workup?
  - Recurrence rates up to 35%
  - Recurrent ipsilateral CN VI paresis- MRI recommended

Conclusions

- In patients ≥ age 50, isolated ocular motor cranial neuropathies are frequently due to microvascular etiology
- Known vascular risk factors include diabetes, hypertension, hypercholesterolemia, coronary artery disease, stroke, smoking
- Controversial whether immediate neuroimaging indicated. If initial neuroimaging deferred, close follow-up is required with MRI brain and orbits with gadolinium at 1-3 months if no improvement or 3-6 months if not resolved