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

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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

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

Risk Factors for Ischemic Ocular Motor Nerve Palsies

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

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
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

Poor diabetic control predisposes to ocular motor cranial nerve paresis

Poor diabetic control predisposes to ocular motor cranial nerve paresis

Diabetes and Hypertension in Isolated Sixth Nerve Palsy
A Population-Based Study Ophthalmology 2005;112:760-763

Case-control study (1978-1992)
- 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)


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 etiologies. Ophthalmology 2013

Is Pain Atypical?

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 severity
- 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?

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
- 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?

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

Long-term Prognosis in Patients With Vasculopathic Sixth Nerve Palsy

Scott K. Sanders, MD, Aki Kawasaki, MD, and Valirir 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 VIP Resolution and Recurrence of Ocular Motor Nerve Microvasculopathies to Vascular Risk Factors

- 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

Workup for Recurrent CN VI Paresis?

- 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

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

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?

- 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)
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

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

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 palsy regardless of whether vascular risk factors are present."

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)
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

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<th>Criteria</th>
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<tr>
<td>Aged &lt; 50</td>
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<td>History of cancer of any type at any time</td>
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<td>Other neurologic signs or symptoms</td>
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<td>Pupil involving or partial cranial nerve VI palsy</td>
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<td>No resolution 3 mo after initial visit</td>
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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