Advances in the Management of Headaches

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Financial Disclosure

• None relevant to the talk
• Attended 2 events in last 12 months where meals were paid by Allergan.
• Equity in Pharmaceutical companies, no products relevant to the talk.
• Investigator for multiple drug trials, no products relevant to the talk.

Educational Need/Practice Gap

• Gap = Inadequate use of prophylactic and acute therapy for patients with primary headache
• Need = Increased awareness of available evidence based treatment options

Objectives

• Identify various headache types.
• Discuss evidence based management strategy for migraine.
• Discuss treatment strategies for cluster headaches.
• Choose an effective treatment strategy for tension-type headaches.

Expected Outcome

• Patients will be appropriately screened for prophylactic therapy
• Patients will receive specific therapy for their headaches
• Minimize the risk associated with use of opioids

Our patient Nancy

• 28 yr old lady presented at 14 years with occasional perimenstrual throbbing headache with associated photo and phonophobia, nausea, and kinesiophobia that last a day.
• Family history of similar headaches in mother and older sister. Lati in her teens had one episode associated with scintillating scotomas prior to the headache.
• After her first and only pregnancy 3 years ago, her headaches started worsening, increasing in frequency and severity, leading to missed work at least two days every month. In addition she has moderate intensity headaches almost 3 to 4 days every week through which she is able to work though with reduced ability.
• Some days she identifies a mild headache for which she takes ibuprofen or combination analgesics with occasional relief.
• Other days she has no relief despite taking multiple doses, took oxycodone with APAP from a friend with mild relief.
• Had to go to the ER where she received morphine and promethazine along with IV fluids.
Likely Diagnosis

- Episodic Migraine Headache
- Chronic Migraine Headache
- Medication overuse headache
- Tension Type Headache
- Chronic Migraine with MOH
- Drug seeking behavior with complaints of headaches

ARS response?

DURATION

<table>
<thead>
<tr>
<th>Short Duration i.e. &lt; 48 hrs</th>
<th>Long Duration i.e. &gt; 48-72 hrs</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigeminal autonomic Cephalalgias</td>
<td>Migraine</td>
<td>Tension Type headache</td>
</tr>
<tr>
<td>Chronic Daily Migraine</td>
<td>Chronic TT Headache</td>
<td>Chronic Migraine with MOH</td>
</tr>
<tr>
<td>Hemicrania Continua</td>
<td>New Daily Persistent Headache</td>
<td></td>
</tr>
</tbody>
</table>

Secondary headaches

- Systemic symptoms (Fever, weight loss, fatigue)
- Secondary risk factors (HIV, cancer, immunodeficiency)
- N Neurologic symptoms/signs (Altered mental status, focal deficits)
- Onset (Split-second, thunderclap)
- Older (New after age 50)
- P Prior history / Positional / Papilledema / Precipitants

Diagnostic criteria: Migraine without aura

- At least 5 attacks fulfilling criteria B-D
- (B) Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- (C) Headache has at least two of the following characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - kinesiophobia
- (D) During headache at least one of the following:
  - nausea and/or vomiting
  - photophobia and phonophobia
- Not attributed to another disorder

Diagnostic criteria: Migraine with aura

- At least 2 attacks fulfilling criteria B-D
- Aura consisting of at least one WITHOUT MOTOR WEAKNESS, SX INCLUDE: VISUAL/SENSORY/DYSPHASIA, ALL FULLY REVERSIBLE
- AT LEAST 2 OF 3
  - Homonymous visual Sx and/or unilateral sensory sx
  - At least 1 aura develops over > 5 min , or different occur in succession > 5 min
  - Each Sx. Last >5 but < 60 min
- Headache meeting criteria 1.1 within 60 minutes
- Not attributed to another disorder
Episodic v/s Chronic migraine

- < 15 days of migraine headaches in a month
- High Frequency EM: 10—15 days/month
- >15 headache days per month for at least 3 months
- Migraine duration up to 72 hours
- 5 migraines/month or once a week

The ER

- patients with migraines treated in the ER
- More patients received opioids as their only anti-headache medication
- Meperidine was the most commonly administered opioid (70%)
- Promethazine and hydroxyzine, anti-emetics without anti-headache effects, were used 6 times more commonly as adjuncts than the dopamine antagonists
- Treatment in ED in 2007
  - 67% received Metoclopramide, Prochlorperazine and Chlorpromazine
  - Followed by opioids (64%)
  - < 10% received specific migraine therapy

Opioids & Migraine

- Headaches treated with opioids have a high rate of recurrence
- Opioids affected response to ketorolac and sumatriptan for 6 months
- rizatriptan was less effective after exposure to opioids.
- it is recommended that opiates/opioids not be used as first-line therapy for migraine pain in the ED or clinic.

Opioids for chronic non-cancer pain

Optimal Therapy for Acute treatment

Supportive
- IV fluids, quiet dark room

Established
- Migraine specific: triptan/ DHE
- Nausea relieving: metoclopramide/chlorpromazine
- Analgesic: NSAID

Emerging
- Nerve blocks
- TMS
TRIPTANS

- CANNOT Combine 2 different triptans within 24 hours
- CAN Combine 2 routes

- Timing
  - Onset of Pain/ Late in aura
  - Prefer non-oral routes
- Contraindicated
  - Vascular disease, or uncontrolled hypertension, ischemic bowel, aneurysm
  - Basilar/hemiplegic migraine
  - Pregnancy Class C

ERGOTS

- Used in the acute treatment of migraine since 1926
- Ergots have high affinity for multiple receptors, potent smooth muscle contractant (blood vessels, uterine)
- Caffeine & Ergotamine: ORAL/RECTAL
- Dihydroergotamine (DHE): NASAL SPRAY
- Dihydroergotamine (DHE-45): IV/IM/SC
- Dihydroergotamine (DHE): orally inhaled DHE, not commercially available

Contraindications

- PREGNANCY CATEGORY X
- Peripheral vascular disease,
- Coronary heart disease,
- Uncontrolled hypertension,
- Stroke,
- Impaired hepatic or renal function,
- Septis
- Complicated migraine, prolonged aura,
- Basilar or hemiplegic migraine.

Dihydroergotamine

- 1986: Raskin compared IV DHE and IV Metoclopramide q8 to IV Diazepam, 2 days with IV DHE to render the patient headache-free then switching to rectal DHE and adding propranolol as a preventive treatment
- 1994: AAN practice guidelines
- 2012: Nagy et al.
  - Delayed component to the improvement in migraine.
  - The data demonstrate a strong predictive effect of good control of nausea, highlighting a practical aspect of management.
  - Up to 11.25 mg over 5 days (not supported by FDA)

Anti-Emetics

- Gastric stasis in migraineurs: interictally & during migraine.
  - (Reduced as well as spontaneous)
- Prochlorperazine
  - Most evidence as good anti-migraine drug
  - 10mg q8h, 40mg daily max- IV, PO, PR
- Metoclopramide
  - 10mg q8h- IV or PO
- Chlorpromazine
  - Sometimes used, some evidence, very sedating
  - 12.5-25mg q6h, 200mg daily max- IV or PO
- Promethazine
  - Weaker as anti-migraine, more sedating as well
  - Ondansetron/ Granisetron
  - No anti-migraine effect, slightly different mechanism of action.
  - Can cause headache on rare occasion.

Magnesium

- NMDA glutamate receptors, modulates the release of substance P, and regulates the production of nitric oxide.
- 3 Studies: 1 g IV had higher pain freedom and 1 study:
  - With aura: Pain and associated symptoms better
  - Without aura: Phosphorus and phosphophilia better
- 4 studies with 2 g IV negative or no benefit
- Almost all / high number of patients experienced brief flushing with magnesium across all studies.
- SAFE IN PREGNANCY

References:
- Kelley, N. E. and Tepper, D. E. (2012), Headache
**IV VALPROATE**

- safe and effective
- similar in effectiveness to DHE/metoclopramide
- initial management of patients with chronic daily headache especially when DHE is ineffective or contraindicated

*Not included* in AAN practice guidelines for acute therapy.

- EFNS guidelines make a mention and suggest “weak evidence”

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**IV Dexamethasone**

- headache recurrence
- dexamethasone 6 mg IV
- dexamethasone 10 mg IV

- Friedman et al compared dexamethasone 10 mg IV *ONLY BENEFIT* in a subgroup where headache duration was more than 72 hours at ED presentation.

- 4 studies compared 15mg to 24 mg dose and oral prednisone : no benefit

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**SUMMARY: “Personal Opinion”**

Migraine specific treatment: Triptan or DHE with premedication

**Consider:** Prochlorperazine, Ketorolac, Magnesium

**Duration >72 hrs**

- Dexamethasone 6-10 mg IV
- IV Valproate infusion
- Chlorpromazine IV 2 mg q 2 min
- Nerve Block

**Supportive care**

- Metoclopramide 10 q 6
- Chlorpromazine 5 q 5 max 25
- Prochlorperazine 10 q 6
- Droperidol (H/A order set)
- Ketorolac 30 IV
- Diclofenac oral
- Dexamethasone 10 mg IV once only

- Ensure diagnosis, Pregnancy status, EKG
- Hydration with NS
- DHE IV/SQ/Nasal
- Imitrex 6 mg SC (may repeat X1)
- Magnesium Sulfate 1gm
- Valproate infusions
- Nerve blocks
- Ketamine (Pain service)
- Lidocaine IV/Nasal Gel 4%

**AED & * Migraine Specific**

**Analgesics**

**Dopamine receptor Antagonist**

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**Nancy**

- was hospitalized as she was unable to get relief from her headache with her medications for 4 days and treated with IV ketorolac, chlorpromazine and dihydroergotamine with good response.

- For moderate to severe intensity headache she now takes prn
  - either sumatriptan oral or injectable along with
    - metoclopramide
    - ketorolac nasal spray or injections

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**Nancy is now in your office**

In addition to PRN rescue medications, she should

- Start prophylaxis with medications
- Botox therapy
- Refer for plastic surgery
- Start birth control
- None of the above
ARS response?

Optimal Prophylaxis

<table>
<thead>
<tr>
<th>Principles</th>
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<tbody>
<tr>
<td>• Complete relief without side effects</td>
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<table>
<thead>
<tr>
<th>Established</th>
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<tbody>
<tr>
<td>• Antiepileptic</td>
</tr>
<tr>
<td>• Beta blockers</td>
</tr>
<tr>
<td>• Anti depressants</td>
</tr>
<tr>
<td>• OnabotulinumtoxinA</td>
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<table>
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<tr>
<th>Emerging</th>
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<tbody>
<tr>
<td>• TENS therapy: Supraorbital, Occipital</td>
</tr>
<tr>
<td>• Peripheral &amp; Cranial Nerve stimulation</td>
</tr>
<tr>
<td>• Deep brain Stimulation</td>
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</tbody>
</table>

AAN Guidelines : Pharmacological

<table>
<thead>
<tr>
<th>Level A (Established efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiepileptic drugs (AEDs)</td>
</tr>
<tr>
<td>• Valproate &amp; topiramate</td>
</tr>
<tr>
<td>• β-Blockers: metoprolol/ propranolol/timolol</td>
</tr>
<tr>
<td>• Frovatriptan for short term prophylaxis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level B (Probably effective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SNRI/SSRI/TCA: Antidepressives</td>
</tr>
<tr>
<td>• β-Blockers: metoprolol  nadolol</td>
</tr>
<tr>
<td>• sumatriptan &amp; zolmitriptan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level C (Possibly effective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ACE inhibitors/Lisinopril/ARA: candesartan</td>
</tr>
<tr>
<td>• β-Blockers: nebivolol/pindolol</td>
</tr>
<tr>
<td>• Cyproheptadine/Carbamazepine/clonidine</td>
</tr>
</tbody>
</table>

AAN Guidelines : Natural / OTC

<table>
<thead>
<tr>
<th>Level A (Established efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Petasites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level B (Probably effective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Magnesium/Riboflavin/Feverfew</td>
</tr>
<tr>
<td>• Histamine inj. sc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level C (Possibly effective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Co Q 10</td>
</tr>
<tr>
<td>• Estrogen</td>
</tr>
</tbody>
</table>

Nancy 1 year later

• Exam is unremarkable except for BMI of 30.3; no papilledema
• Previous trials of meds include
  • amitriptyline: caused dry mouth, weight gain and sedation and was not very helpful
  • topiramate: interfered with her work as a school teacher
  • propranolol: made her tired and not very helpful but she continues
• The patient presented with a headache calendar for the past 3 months with average of 17 to 20 days of moderate or severe intensity pain and 5 days of mild intensity pain.

Next steps

• Refer for Botox therapy
• Refer for Bariatric surgery
• Refer to Plastic surgery
• Refer to Pain Clinic
• Just refer….!
Episodic Migraine & OnabotulinumtoxinA


OnabotulinumtoxinA in Chronic Migraine

- PREEMPT 1 Jan 2006 to July 2008, at 56 North American sites
- PREEMPT 2 Feb 2006 to Aug 2008, at 66 global sites (50 North American and 16 European)


Lipton R et al. Neurology 2011;77:1465-1472

Next Steps for Nancy

- Lack of strong evidence limits acceptance by insurance
- We offered counselling, reinforced correct lifestyle changes
- Offered and completed nerve blocks
- Information regarding investigational options, not currently approved by the FDA

Nancy 1 year later

- Received 12 months of onabotulinumtoxinA therapy as per FDA approved protocol but did not perceive a clear benefit.
- Insurance declined continued use
- She has become increasingly depressed, anxious & gaining weight
- She identifies a persistent nagging pain in the back of her head with tenderness on examination
Emerging Interventions

Nerve blocks
TENS therapy: Supraorbital, Occipital
Peripheral & Cranial Nerve stimulation
Transcranial Magnetic Stimulation
Surgical decompression of Peripheral nerve sites
Deep brain Stimulation

Nerves for pain relief

- Greater Occipital Nerve
- Lesser Occipital Nerve
- Auriculotemporal Nerve
- Supraorbital Nerve
- Sphenopalatine ganglion

Nerve Blocks consensus

- Experience and research suggest efficacy
- Effect on head pain may outlast its anesthetic effect
- Occipital tenderness predicts favorable outcome
- Safe and usually well-tolerated
- No evidence for an added beneficial effect of corticosteroids (exception: cluster headache) to ON blocks
- More controlled studies needed

Contraindications

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Concerns</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthetic allergy</td>
<td>Allergic reactions, including anaphylaxis</td>
<td>Prolong with local anesthetic concomitantly</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hypotension</td>
<td>Use caution, monitor closely</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Nephrectomy</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Prior neurovascular attacks</td>
<td>Neurapraxia or nerve injury</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Open skull defect</td>
<td>Intracranial pressure rise</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Anticoagulation therapy</td>
<td>Hemorrhage</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Connective tissue defects</td>
<td>Atlantoaxial instability</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

Sphenopalatine Ganglion NB
If you can’t block them, then stimulate them!

Supraorbital/Supratrochlear Transcutaneous NS for Migraine prophylaxis


Pain-free 2 hours after treatment

TMS (82)
Sham (82)

*P<0.018

SPF 24 and 48 hours after treatment

24h
48h

*P<0.040
**P<0.033

Single Pulse Transcranial Magnetic Stimulation (TMS): Acute treatment of Migraine

Peripheral & Cranial Nerve stimulators

• Occipital Nerve stimulators
• Supraorbital Nerve Stimulators
• Migraine
• Chronic Daily Headache
• Combination approaches
• Trigeminal Autonomic Cephalalgias

NOT FDA APPROVED

DBS in headaches

Nancy asked Siri!

The New York Times
Plastic Surgery May Also Ease Migraines
May Hemp
By CHRISTINE GEIER
12/18/2015
Surgical deactivation for Migraine

Conclusion: Based on the 5-year follow-up data, there is strong evidence that surgical manipulation of one or more migraine trigger sites can successfully eliminate or reduce the frequency, duration, and intensity of migraine headache in a lasting manner. (Plast. Reconstr. Surg. 127: 603, 2011.)

Although the percentage of patients who observed complete elimination of migraine headache is not substantial in this study….

In light of recent news reports about the growing use of surgical intervention in migraine, the American Headache Society urges patients, healthcare professionals and migraine treatment specialists themselves, to exercise caution in recommending or seeking such therapy. In our view, surgery for migraine is a last-resort option and is probably not appropriate for most sufferers. To date, there are no convincing or definitive data that show its long-term value.

SUMMARY: CHRONIC MANAGEMENT

ESTABLISH CHRONIC MIGRAINE, Rx medically
EXCLUDE OTHER DIAGNOSIS, (INDOMETHACIN TRIAL)
BOTOX TRUE REFRACTORY
TREAT WITH DHE IF POSSIBLE
TREAT WITH DHE IF POSSIBLE
true-refractory
TENSION/NERVE DECOMPRESSION

John....

Is 38, who has enjoyed good health, has no significant history of headaches till about a year ago. Over the past year, he has developed month long periods of daily eye pain, like sharp stabbing. He paces around to get comfortable but cannot. The episode is self limited for an hour but very disabling when it hits. He has a few months with no pain and then it returns and recurs like clockwork.

Nancy....

Has gradually adjusted to her stress, has a new friendly team of coworkers, increased her exercise, reduced her caffeine and with time, made improvements with her headaches. Pleased she referred her brother John to us.....
Trigeminal Autonomic Cephalalgias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Duration</th>
<th>Frequency</th>
<th>Migraine Features?</th>
<th>Gender (F:M)</th>
<th>Indocin response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster</td>
<td>15-180 min</td>
<td>Every other day to 8/day</td>
<td>Sometimes</td>
<td>1.3-7</td>
<td>+/-</td>
</tr>
<tr>
<td>Paroxysmal Hemicrania</td>
<td>2-30 min</td>
<td>1-2/day</td>
<td>Sometimes</td>
<td>2.3-1</td>
<td>Yes</td>
</tr>
<tr>
<td>SUNA</td>
<td>2-600 sec</td>
<td>Dozens to hundreds per day</td>
<td>Sometimes</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>SUNCT</td>
<td>5-240 sec</td>
<td>Dozens to hundreds per day</td>
<td>No</td>
<td>1:2</td>
<td>No</td>
</tr>
</tbody>
</table>

Cluster Headache

A. At least five attacks fulfilling criteria B-D:
B. Severe or very severe unilateral, supraorbital and/or temporal pain lasting 15-180 min (when untreated)
C. Either or both of the following:
   1. At least one of the following symptoms or signs, ipsilateral to the headache:
      a) conjunctival injection and/or lacrimation
      b) nasal congestion and/or rhinorrhea
      c) eyelid oedema
      d) forehead and facial sweating
      e) sensation of fullness in the ear
      f) miosis and/or ptosis
   2. A sense of restlessness or agitation
D. Attacks have a frequency between one every other day and 8 per day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis.

Cluster Headache Acute treatment

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan SC</td>
<td>Sumatriptan nasal</td>
<td>Civamide nasal</td>
</tr>
<tr>
<td>Zolmitriptan Nasal</td>
<td>Zolmitriptan oral</td>
<td>Divalproex</td>
</tr>
<tr>
<td>100% Oxygen for 15 minutes</td>
<td>Lidocaine Nasal (C)</td>
<td>GON Blocks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melatonin</td>
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</tbody>
</table>

Cluster Headache Prophylaxis

<table>
<thead>
<tr>
<th>Level B</th>
<th>Level C</th>
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<tbody>
<tr>
<td>Civamide nasal</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Lithium</td>
</tr>
<tr>
<td>GON Blocks</td>
<td>Melatonin</td>
</tr>
</tbody>
</table>

SPG stimulation for Acute cluster treatment

FOR INVESTIGATIONAL USE

John’s wife ....

Is 36, also has headaches, mild to moderate intensity dull aching pain at the back of her head, many days at a time. She does not get nauseous and is not light or noise sensitive. She claims to have a high pain threshold, blames it on the stress of running a household with three kids in addition to staying busy with work. Some days she will take an OTC ibuprofen with some benefit. Most days, she will tough it out.
Tension Type Headache

- Headache 30 minutes - 7 days
- Headache has at least 2 of the following characteristics:
  - Bilateral location
  - Pressing/tightening (non-pulsating) quality
  - Mild or moderate intensity
  - Not aggravated by routine physical activity such as walking or climbing stairs
- Both of the following:
  - No nausea or vomiting (anorexia may occur)
  - No more than one of photophobia or phonophobia

Treatment

- Triptans alleviate TTH attacks in person with Migraine but not in pure TTH (Spectrum study)
- Triptans, muscle relaxants and opioids should not be used in pure TTH.
- Avoid frequent and excessive use of analgesics to prevent the development of medication-overuse headache.
- Amitriptyline is drug of choice for the prophylactic treatment of chronic TTH (LEVEL A; EFN) .
- Mirtazapine and venlafaxine are drugs of second choice.
- Non Pharmacologic treatment: PT, CBT

Summary

- Effective treatments exist for many primary headache disorders, reducing disability.
- Specific acute treatments are preferred over non specific analgesic treatment.
- Frequent acute treatment should lead to initiation of prophylactic therapy.
- Advanced treatment options are available for refractory patients.
- Opioids are deleterious for headaches should be avoided for headache.

Thank You

Q & A
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