WAKE-UP/UNKNOWN SYMPTOM ONSET STROKE PROCESS

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Thrombolytic Therapy

- Patients must meet inclusion/exclusion screening criteria and present for treatment less than 3 hours from symptom onset time
  - *AHA/ASA recommend extending the treatment window to 4.5 hours for eligible patients*

- Statistically only 3 to 5 % of those who suffer a stroke receive treatment with thrombolytic therapy

- One of the reasons for no treatment is *"Unknown symptoms onset"*

(Benjamin, et al., 2019)

Overview

- Stroke is currently the 5th leading cause of death and the leading cause of serious long-term disability in the United States (Benjamin et al., 2019)
- Early recognition of symptoms and early intervention provides the best opportunity for good outcomes
- In 14 to 27% of patients, the onset of symptoms is unknown (Thomalla et al., 2018)
- Patients outside the 4.5-hour window are excluded from thrombolytic treatment due to the increased risk of intracranial hemorrhage
- Over the past 10 years, researchers have been attempting to identify a way to use advanced imaging to determine a timeline for wake-up stroke (WUS) and unknown symptom onset stroke (Barreto et al., 2009; Manawadu et al., 2013a; Manawadu et al., 2013b; Schwamm et al., 2018; Thomalla et al., 2018).
- MRI has been determined to be a safe and feasible intervention to determine the timing of symptoms allowing WUS and unknown symptom onset stroke patients to receive thrombolytic treatment (Schwamm et al., 2018; Thomalla et al., 2018).

Overview Continued…

- In a large population study, stroke onset was found to be higher in the morning hours between 6am and 12p peaking around 8:30am and minimal occurring during the night
- A meta-analysis of 31 studies showed a 49% increased risk of stroke between 6am and 12p
- The use of MRI for wakeup and unknown onset stroke was added to the 2019 AHA/ASA Guidelines as a IIa recommendation

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

3. In patients with AIS who awake with stroke symptoms or have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.	**IIa**	**B-R**

The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) randomized 503 patients with AIS who awoke with stroke or had unclear time of onset >4.5 hours from last known well and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the middle cerebral artery (MCA), NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. The trial was terminated early for lack of funding before the designated 800 patients were randomized. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well was slightly over 10 hours. At baseline, one-third of the patients had vessel occlusion on time-of-flight MRA, and three-quarters of the FLAIR lesions were <9 mL. The end point of an mRS score of 0 to 1 at 90 days was achieved in 53.3% of the IV alteplase group and in 41.8% of the placebo group (P=0.02).[88]

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL B-R — **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR.	**IIa**	**B-R**	**CLASS IIa (MODERATE) — Benefit >> Risk** Suggested phrases for writing recommendations: ▪ Is reasonable ▪ Can be useful/effective/beneficial ▪ Comparative-Effectiveness Phrases†: ○ Treatment/strategy A is probably recommended/indicated in preference to treatment B ○ It is reasonable to choose treatment A over treatment B **LEVEL B-R — (Randomized)** ▪ Moderate-quality evidence‡ from 1 or more RCTs ▪ Meta-analyses of moderate-quality RCTs
The WAKE-UP RCT randomized 503 patients with AIS who awoke with stroke or had unclear time of onset and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the MCA, NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well to symptom recognition was ≈7 hours and to alteplase administration slightly over 10 hours. The primary end point of an mRS score 0 to 1 at 90 days was achieved in 53.3% of the alteplase group and in 41.8% of the placebo group (*P*=0.02). Only 20% had LVO of the intracranial internal carotid or proximal middle cerebral arteries.[88]			

Stroke Association. A division of the American Heart Association.

Terms

- Last Known Normal/Last Known Well/Last Seen Normal – the date and time that the patient (if able to communicate) or a witness can confirm the patient was at their baseline prior to the current stroke symptoms

- Onset Time/Time of Stroke Onset – the date and time when the stroke symptoms were witnessed to occur (patient was at their baseline and then suddenly began with symptoms)

- Time Symptoms Recognized/Time Symptoms Noted/Time of Symptom Discovery – the date and time at which the stroke symptoms were first noticed by a reliable witness, or the patient noticed the symptoms upon awakening

- Wake-up Stroke (WUS) Patient – a patient who awakens from sleep with active stroke/stroke-like symptoms

- Unknown Symptoms Onset (USO) Patient – a patient who is experiencing stroke/stroke-like symptoms and is unable to communicate and there is no family/friend that can clearly state when the symptoms first started

Stroke Code Process Summary

- Early recognition, Stroke Code activation and VAN screening
- The priority for these patients remain early CT to rule out hemorrhage
- Patients with suspected LVO (VAN +) should undergo CTA before any MRI imaging to determine eligibility for early endovascular therapy (Mechanical Thrombectomy)
- Patients with developing core infarct seen on non-contrast CT are not eligible for WUS/Unknown Symptom Onset Stroke Protocol
- Patient who have other identified contraindications to thrombolytic therapy do not meet the protocol
- Time goals remain the same – early administration of thrombolytic therapy

**It is well established that the MRI Acute Protocol will cause some delays due to resources and distance – a well established process will limit the impact of these barriers

MRI for WUS/Unknown Symptom Onset Stroke

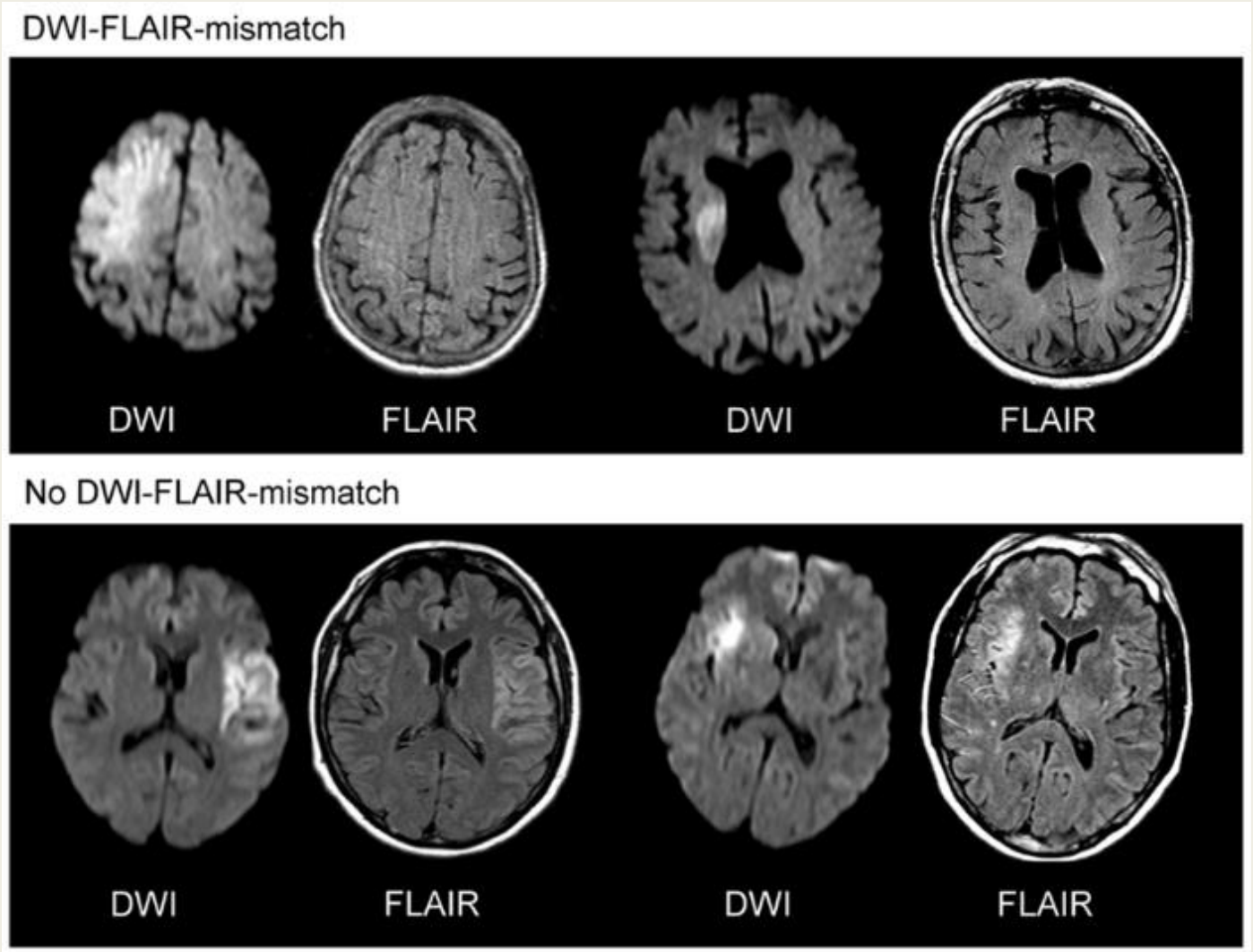
- Diffusion Weighted Image (DWI)
  - *MRI sequence that looks at the diffusion of water. Diffusion of water in infarcted tissue will be restricted causing the image to show a hyperintensity in the region of involved tissue (Baliyan, Das, Sharma, & Gupta, 2016). DWI lesions will be used to identify acute stroke, as changes can be seen within minutes of a stroke.*

- Fluid Attenuated Inversion Recovery (FLAIR)
  - *An MRI sequence that is highly sensitive to subacute ischemic brain lesions (Thomalla et al., 2011). Changes on FLAIR occur over time and will be used to assist in the identification of strokes that are older than four hours.*

- DWI-FLAIR Mismatch
  - *Term used to describe the identification of infarcted tissue on DWI, but no evidence on FLAIR suggesting the infarct is within four hours (Thomalla et al., 2011). DWI-FLAIR mismatch will be used to determine if the patient's acute stroke symptoms are less than or greater than four hours.*

- **Patients with a DWI-FLAIR Mismatch and no other contraindications should be considered for thrombolytic therapy.**

DWI/FLAIR Mismatch



(Rimmele & Thomalla, 2014)

How to Order Correct MRI

- OLD order
  - *MRI BRAIN ISCHEMIC INTERVENTIONAL PROTOCOL INCL MRA W/O CONTRAST (XPD) [IMG5107]*

- New order **OMCNO ONLY**
  - *MRI Wake-up/Unknown Onset STROKE CODE/NIR Evaluation (XPD [IMG6006]*

- Community Hospitals as well as Shreveport and Lafayette
  - *New order build in progress*
  - *Can use old order if available at your site*

****This particular MRI should ONLY be used to determine eligibility for Thrombolytic therapy (or IR if used at OMCNO) – rationale: this particular MRI protocol is a limited study and does not include all of the normal sequences in a regular MRI which may be needed to fully evaluate the patient's symptoms*

Case Review #1

- 56 y/o male with HTN, HLD, DM2, Tobacco abuse presented with slurred speech and right sided weakness. Patient reports going to sleep last night feeling like his normal self around 11:00pm. He awoke at 6:00am this morning with symptoms. He notified his wife but he refused to let her call 911. She drove him to the ED and he arrived at 6:45am. Triage nurse notices slurred speech and obvious right sided weakness.

- What is the Last Known Normal?
- What is the Onset Time?
- What is the Symptom Recognition Time?

- Would you activate a Stroke Code?

Case Review #1

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- What is the Last Known Normal? ***11:00pm***
- What is the Onset Time? ***Unknown***
- What is the Symptom Recognition Time? ***6:00am***

- Would you activate a Stroke Code? ***Yes – patient is a Wakeup Stroke within 4.5 hours of Symptom recognition and could be eligible for thrombolytic therapy***

Case Review #2

- Same patient except in this scenario the patient refused to let his wife call 911 and instead decided to lay back down to see if the symptoms would improve. When he awoke at 10:00am the symptoms were still present. He decided to let his wife drive him to the ED at this time. He arrived at 11:30am.

- What is the Last Known Normal?
- What is the Onset Time?
- What is the Symptom Recognition Time?

- Would you activate a Stroke Code?

Case Review #2

- Same patient except in this scenario the patient refused to let his wife call 911 and instead decided to lay back down to see if the symptoms would improve. When he awoke at 10:00am the symptoms were still present. He decided to let his wife drive him to the ED at this time. He arrived at 11:30am.

- What is the Last Known Normal? ***11:00pm***
- What is the Onset Time? ***Unknown***
- What is the Symptom Recognition Time? ***6:00am***

- Would you activate a Stroke Code? ***No – unfortunately, the patient arrived > 4.5 hours which makes him ineligible for thrombolytic therapy***

Case Review #3

- 78 y/o female with afib (not on AC), HTN, HLD is brought in by EMS after being found by family confused and not moving her right side. She lives alone and the daughter states she spoke with the patient last week and at that time patient seemed to be acting normal. The daughter found the patient with symptoms at 2:00pm. She arrives to the ED at 2:20pm. The patient is unable to communicate.

- What is the Last Known Normal?
- What is the Onset Time?
- What is the Symptom Recognition Time?

- Would you activate a Stroke Code?

Case Review #3

- 78 y/o female with afib (not on AC), HTN, HLD is brought in by EMS after being found by family confused and not moving her right side. She lives alone and the daughter states she spoke with the patient last week and at that time patient seemed to be acting normal. The daughter found the patient with symptoms at 2:00pm. She arrives to the ED at 2:20pm. The patient is unable to communicate.

- What is the Last Known Normal? ***1 week ago***
- What is the Onset Time? ***Unknown***
- What is the Symptom Recognition Time? ***2:00pm***

- Would you activate a Stroke Code? ***Yes, the patient is an unknown symptom onset patient arriving within 4.5 hours of symptom recognition***

Case Review #3 Continued…

- After you activated the Stroke Code, you did a quick VAN assessment and confirmed the patient has right sided weakness, aphasia, and a right field cut. The patient has been evaluated by the ED provider who also confirmed these exam findings. CT head has been completed which did not show any early infarct signs or hemorrhage. The patient does not have any exclusion for thrombolytic therapy

- What is the next imaging?

Case Review #3 Continued…

- After you activated the Stroke Code, you did a quick VAN assessment and confirmed the patient has right sided weakness, aphasia, and a right field cut. The patient has been evaluated by the ED provider who also confirmed these exam findings. CT head has been completed which did not show any early infarct signs or hemorrhage. The patient does not have any exclusion for thrombolytic therapy

- What is the next imaging? ***CTA head and neck – even though the patient meets criteria for MRI protocol the patient is VAN + so LVO needs to be rule out first***

Summary

- WUS/Unknown symptom onset stroke patients presenting within 4.5 hours of symptom recognition should have a Stroke Code activation
- CT head still first line imaging to rule out hemorrhage
- VAN+, suspected LVO should have CTA before proceeding to MRI
- Confirmed LVO patients should still get MRI imaging if feasible but SHOULD NOT delay transfer
- MRI is recommended in the ASA Guidelines (there is research supporting the use of CT perfusion as well so this modality is acceptable) (Rarely will CT head alone be used, but at discretion of Neurologist)
- Patients “found down” or found with symptoms who arrive to the ED within 4.5 hours of symptom recognition should have a Stroke Code activation regardless of when their Last Known Normal time is

References

- Barreto, A. D., Martin-Schild, S., Hallevi, H., Morales, M. M., Abraham, A. T., Gonzales, N. R., Illoh, K., Grotta, J., & Savitz, S. I. (2009). Thrombolytic therapy for patients who wake-up with stroke. *Stroke, 40*, 827-832.
- Benjamin, E. J., Muntner, P., Alonso, A., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Change, A. R., Cheng, S., Das, S. R., Delling, F. N., Djousse, L., Elkind, M. S., Ferguson, J. F., Fornage, M., Jordan, L. C., Khan, S. S., Kissela, B. M., Knutson, K. L., … Virani, S. S. (2019). Heart disease and stroke statistics-2019 Update: a report from the American Heart Association. *Circulation, 139*, e1-e473.
- Manawadu, D., Bodla, S., Jarosz, J., Keep, J., & Kalra, L. (2013a). A case-controlled comparison of thrombolysis outcomes between wake-up and known time of onset ischemic stroke patients. *Stroke, 44*, 2226-2231.
- Manawadu, D., Bodla, S., Jarosz, J., Keep, J., & Kalra, L. (2013b). An observational study of thrombolysis outcomes in wake-up ischemic stroke patients. *Stroke, 44*, 427-431.
- Peter-Derex, L., & Derex, L. (2019). Wake-up stroke: From pathophysiology to management. *Sleep medicine reviews*, *48*, 101212.
- Rimmele, D., & Thomalla, G. (2014). Wake-up stroke: clinical characteristics, imaging findings, and treatment option – an update. *Frontiers in Neurology, 5*(35).
- Schwamm, L. H., Wu, O., Song, S., Latour, L., Ford, A. L., Hsia, A. W., Muzikansky, A., Betensky, R. A., Yoo, A. J., Lev, M. H., Boulouis, G., Lauer, A., Cougo, P., Copen, W. A., Harris, G. J., & Warach, S. (2018). Intravenous thrombolysis in unwitnessed stroke onset: MR WITNESS trial results. *Annals of Neurology, 83*, 980-993.
- Thomalla, G., Simonsen, C. Z., Boutitie, F., Andersen, F., Berthezene, Y., Cheng, B., Cheripelli, B., Cho, T., Fazekas, F., Fiehler, J., Ford, I., Galinovic, I., Gellissen, S., Golsari, A., Gregori, J., Gunther, M., Guibernau, J., Hausler, K. G., Hennerici, M., … Gerloff, C. (2018). MRI-guided thrombolysis for stroke with unknown time of onset. *The New England Journal of Medicine, 379*(7), 611-622.