SEMPI Priority clinical area: Neuroimaging

INTRODUCTION

Headache (Traumatic and Non-traumatic)

Headache (HA) is one of the most common presenting symptoms evaluated by primary care, neurology, and emergency room providers as well as a leading cause of morbidity/mortality worldwide (Feigin et al., 2017). The decision to perform/not perform neuroimaging in patients with headache represents a frequent diagnostic challenge. To facilitate the assessment and management of these patients, it is important to categorize headaches as **primary** or **secondary**. More than 90% of headaches are considered primary, and less than 10% are secondary (Wilson, 1991; Evans, 1996). Primary headaches include tension-type headaches, migraines and cluster headaches. These headache types are not caused by any underlying condition. In the case of **primary** headaches which are often recurrent, neuroimaging is generally not required as the HA itself is the disorder (i.e., no underlying cause) (Mullally & Hall, 2018). Conversely, **secondary** headaches (e.g., infection, bleeding, mass lesion-related) warrant imaging studies to identify an underlying process that results in brain pathology. The differentiation between primary and secondary HA disorders is based upon clinical assessment requiring a thorough history and neurologic exam. Several "warning" signs/"red flag" symptoms have been identified that are associated with a high likelihood of underlying intracranial lesions or brain pathology (**secondary** headache category) and thus warrant neuroimaging as recommended by Dodick (2003) and Kumar & Cooney (1995):

- Sudden onset ('thunderclap'); severity— "Worst headache ever"
- Headache with signs of systemic illness (infection, malignancy, bleeding/coagulopathy)
- New headache and abnormal exam findings (focal neurologic deficits, lack of coordination, altered level of consciousness)
- New headache in pregnancy
- New headache in patients aged 50 years or older
- New headache in immunocompromised patient (+HIV, chemotherapy treatment)
- Headache with associated seizures
- Change in headache pattern or progressive worsening despite conservative therapy
- Onset of headache with exertion, Valsalva, cough, change in position
- Signs of increased intracranial pressure—projectile vomiting, papilledema
- Atypical cluster HA presentation when other trigeminal autonomic syndromes suspected (e.g. paroxysmal hemicrania, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing [SUNCT])

Advanced Imaging Modalities

The importance of a careful neurologic exam in delineating primary from secondary HA is supported by literature reporting that patients with positive history and abnormal physical findings are much more likely to have significant brain pathology as detected by MR/CT imaging compared to patients with normal neurologic exams (Mitchell et al., 1993). The yield of neuroimaging is very low if no high-risk historical feature is present and the neurologic examination is normal (Evan, 1996; Sempere et al., 2005). Nonetheless, the decision to scan or not to scan in the setting of HA remains one of clinical judgment as there are no randomized, controlled trials that specifically indicate when neuroimaging is indicated (or when it is not). Further, it is unlikely that such data will be available in the future as blinding and randomization to conduct such studies pose ethical hurdles. Differences exist in the indications for various imaging techniques. For example, MR provides greater detail and is generally more sensitive than CT imaging for detecting edema, vascular lesions, tumors, and other types of intracranial pathology, particularly in the posterior fossa. On the other hand, CT is more widely available, less costly, and more expeditious in urgent settings when concern for hemorrhage, infection, or traumatic injury is high. CT is preferred when subarachnoid hemorrhage (SAH) is suspected (followed by lumbar puncture in some cases). However, it should be noted that timing of the CT scan can be critical; when done within 6 hours of 'worst HA in my life/thunderclap' HA presentation, sensitivity for SAH was 100% but fell to 93% when done after 6 hours (Perry et al., 2011). Alternately, MR is more sensitive in "late" identification of SAH (> 4 days) (Mitchell et al., 2001).

Diagnostic strategies vary with different secondary HA etiologies. For example, if temporal arteritis is suspected, an ultrasound of the temporal artery may or may not be performed to facilitate a biopsy of the vessel. In pregnancy, HA symptoms should prompt neuroimaging especially when abnormal neurologic exam findings are present since a high incidence of venous thrombosis, pseudotumor cerebri, and intracranial hemorrhage is reported (Ramchandren et al., 2007). MR may be preferred in this setting over CT given its absence of radiation exposure. Angiography is recommended only after other non-invasive imaging has indicated a definite suspicion of tumor, vasculitis, aneurysm or other vascular malformation (Rothner, 1991). Methods to evaluate cerebral artery lumens traditionally include computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). Once a diagnosis of SAH has been made, the etiology of the hemorrhage can be determined by any of these methods (Westerlaan et al., 2011). All three methods can evaluate the veins, but CT venography (CTV) and MR venography (MRV) are traditionally done separately from CTA and MRA. Gadolinium-enhanced MRV is now the "gold standard" in the evaluation of the cerebral venous system (Agid et al., 2008).

Cognitive Disorders/Dementia

Dementia/Major Neurocognitive Disorder (NCD) (DSM-5 2013) is a clinical diagnosis characterized by cognitive decline in one or more domains (e.g., learning and memory, language, executive function, complex attention, perceptual-motor, or social behavior) that represents a change from prior levels of function and is severe enough to interfere with daily living and independence (Regier et al., 2013). The most common form

of dementia, Alzheimer's disease dementia (ADD), accounts for approximately 60-80% of all cases; other forms of dementia include dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD), frontotemporal dementia (FTD), and vascular dementia. The hallmark of dementia (major NCD), irreversible cognitive impairment, carries high socioeconomic costs due, in part, to increasing prevalence with advancing age and demographic shifts to an older population. In 2010, worldwide costs of care exceeded 600 billion dollars; 2015 estimates of global prevalence of dementia range from 45-50 million which is expected to double by 2030 (World Health Organization, 2017). The diagnosis of dementia (major NCD) is a **clinical** one, neuroimaging may be used as part of a comprehensive evaluation to either differentiate one type of dementia from another in ambiguous cases, rule out reversible causes, or as a research tool. Neuroimaging cannot be used as a "stand-alone" diagnostic test for dementia. There are three categories of neuroimaging that can be used to evaluate cognitive impairment including **structural**, **functional**, and **molecular**. Structural imaging (computed tomography-**CT** or magnetic resonance imaging-**MR**) can be done as part of an initial evaluation to determine the degree/location of brain atrophy and to exclude reversible processes causing cognitive impairment (e.g., space-occupying lesions, chronic subdural hematoma, or hydrocephalus). Conversely, functional (glucose-metabolism, dopaminergic activity) and molecular (beta-amyloid or tau protein) imaging, utilizing positron emission tomography (**PET**) or single photon emission computed tomography (**SPECT**), are done in selected patients when further diagnostic differentiation is needed, or dictated by investigational protocols in tertiary referral centers.

Clinical Diagnosis:

Clinical assessment for the diagnosis of dementia can be highly accurate when performed by clinical experts in patients who present with neurocognitive symptoms (Health Quality Ontario, 2014). There are multiple evaluations tools designed to aid in the diagnosis of dementia. Among the most commonly used neurocognitive assessments are the Mini-Mental Status Examination (MMSE), Mini-Cog test, Addenbrooke's Cognitive Examination-Revised (ACE-R) and the Montreal Cognitive Assessment (MoCA).

Structural Neuroimaging:

Computed tomography (CT) and magnetic resonance imaging (MR) can be used to identify global as well as regional brain atrophy associated with neurodegenerative diseases (e.g., disproportionate hippocampal atrophy in Alzheimer's disease). Structural imaging can also identify reversible causes of impaired cognition including space-occupying-lesions (tumor, abscess, chronic subdural hematoma), cerebrovascular disease (ischemic/hemorrhagic stroke, aneurysm), or hydrocephalus. Structural imaging (CT/MR) without contrast enhancement can be performed as part of the initial evaluation for patients with neurocognitive symptoms, however, repeated neuroimaging to monitor the progression of the disease is not recommended (Health Quality Ontario, 2014).

Functional and Molecular Neuroimaging:

Functional neuroimaging can demonstrate reduced/absent glucose metabolism in defined anatomic areas of the brain that correlate with specific types of dementia (e.g., hippocampus, temporal/parietal lobes and Alzheimer's dementia) using radio-labelled glucose and positron

emission tomography (^{18}fluorodeoxyglucose[FDG]-PET). Molecular imaging identifies accumulation of toxic proteins (β-amyloid or neurosynaptic injury (tau protein) associated with specific types of dementia, using radio-labelled tracers (e.g.^{18}F-florbetapir for amyloid) and PET imaging. Both functional and molecular neuroimaging (FDG-PET, amyloid-PET) remain largely investigational, limited to research center protocols, and prohibitively costly. Professional society guidelines for use of amyloid-PET in patients with neurocognitive symptoms have recently been published and limit indications for its use to patients with atypical presentations (Johnson et al., 2013). Low or absent dopaminergic activity in the striatum (e.g., substantia nigra, putamen) on ^{123}I-ioflupane-dopamine transporter single photon emission CT (SPECT) imaging is characteristic of both Parkinson disease dementia and Lewy body dementia. Again, SPECT imaging is not widely available and not indicated for routine use.

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