single stab or a series of stabs; absence of associated cranial autonomic features; absence of cutaneous triggering of attacks; and a pattern of recurrence at irregular intervals (hours to days). The pains have been variously described as "ice-pick pains" or "jabs and jolts." They are more common in patients with other primary headaches, such as migraine, the TACs, and hemicrania continua.

TREATMENT **PRIMARY STABBING HEADACHE**

The response of primary stabbing headache to indomethacin (25–50 mg two to three times daily) is usually excellent. As a general rule, the symptoms wax and wane, and after a period of control on indomethacin, it is appropriate to withdraw treatment and observe the outcome.

Nummular Headache Nummular headache is felt as a round or elliptical discomfort that is fixed in place, ranges in size from 1–6 cm, and may be continuous or intermittent. Uncommonly it may be multifocal. It may be episodic but is more often continuous during exacerbations. Accompanying the pain there may be a local sensory disturbance, such as allodynia or hypesthesia. Local dermatologic or bony lesions need to be excluded by examination and investigation. This condition can be difficult to treat; tricyclics, such as amitriptyline, or anticonvulsants, such as topiramate or valproate, are most often tried.

Hypnic Headache This headache syndrome typically begins a few hours after sleep onset. The headaches last from 15 to 30 min and are typically moderately severe and generalized, although they may be unilateral and can be throbbing. Patients may report falling back to sleep only to be awakened by a further attack a few hours later; up to three repetitions of this pattern occur through the night. Daytime naps can also precipitate head pain. Most patients are female, and the onset is usually after age 60 years. Headaches are bilateral in most, but may be unilateral. Photophobia, phonophobia, and nausea are usually absent. The major secondary consideration in this headache type is poorly controlled hypertension; 24-h blood pressure monitoring is recommended to detect this treatable condition.

TREATMENT **HYPNIC HEADACHE**

Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg). For those intolerant of lithium, verapamil (160 mg) or methysergide (1–4 mg at bedtime) may be alternative strategies. One to two cups of coffee or caffeine, 60 mg orally, at bedtime may be effective in approximately one-third of patients. Case reports also suggest that flunarizine, 5 mg nightly, can be effective.

New Daily Persistent Headache Primary new daily persistent headache (NDPH) occurs in both males and females. It can be of the migrainous type, with features of migraine, or it can be featureless, appearing as new-onset TTH. Migrainous features are common and include unilateral headache and throbbing pain; each feature is present in about one-third of patients. Nausea, photophobia, and/or phonophobia occur in about half of patients. Some patients have a previous history of migraine; however, the proportion of NDPH sufferers with preexisting migraine is no greater than the frequency of migraine in the general population. At 24 months, ~86% of patients are headache-free. Treatment of migrainous-type primary NDPH consists of using the preventive therapies effective in migraine (see above). Featureless NDPH is one of the primary headache forms most refractory to treatment. Standard preventive therapies can be offered but are often ineffective. The secondary NDPHs are discussed elsewhere (Chap. 21).

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ALZHEIMER'S DISEASE

Approximately 10% of all persons over the age of 70 years have significant memory loss, and in more than half, the cause is Alzheimer's disease (AD). It is estimated that the median annual total cost of caring for a single patient with advanced AD is >$50,000, while the emotional toll for family members and caregivers is immeasurable. AD can manifest as young as the third decade, but it is the most common cause of dementia in the elderly. Patients most often present with an insidious loss of episodic memory followed by a slowly progressive dementia that evolves over years. In typical amnestic AD, brain imaging reveals atrophy that begins in the medial temporal lobes before spreading to lateral and medial parietal and temporal lobes and lateral frontal cortex. Microscopically, there are neuritic plaques containing amyloid beta (Aβ), neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau filaments, and Aβ accumulation of in blood vessel walls in cortex and leptomeninges (see "Pathology," below). The identification of causative mutations and susceptibility genes for AD has provided a foundation for rapid progress in understanding the biological basis of the disorder. The major genetic risk for AD is apolipoprotein ε4 (Apo ε4). Carrying one E4 allele increases the risk for AD by 2- to 3-fold, whereas two alleles increase the risk 16-fold.

CLINICAL MANIFESTATIONS

The cognitive changes of AD tend to follow a characteristic pattern, beginning with memory impairment and progressing to language and visuospatial deficits. Yet, approximately 20% of patients with AD present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. In other patients, upstream visual processing dysfunction (referred to as posterior cortical atrophy syndrome) or a progressive "logopenic" aphasia are the primary manifestations of AD for years before progressing to involve memory and other cognitive domains. Still other patients may present with an asymmetric akinetic-rigid-dystonic ("corticobasal") syndrome or a dysexecutive "frontal variant" of AD.

In the early stages of typical amnestic AD, the memory loss may go unrecognized or be ascribed to benign forgetfulness of aging. Once the memory loss becomes noticeable to the patient and spouse and falls 1.5 standard deviations below normal on standardized memory tests, the term mild cognitive impairment (MCI) is applied. This construct provides useful prognostic information, because approximately 50% of patients with MCI (roughly 12% per year) will progress to AD over 4 years. Increasingly, the MCI construct is being replaced by the notion of "early symptomatic AD" to signify that AD is considered the underlying disease (based on clinical or biomarker evidence) in a patient who remains functionally compensated. Even earlier in the course, "prodromal AD" refers to a person with biomarker evidence of AD (amyloid imaging positive with positron emission tomography or low cerebrospinal $A\beta_{42}$ and mildly elevated tau) in the absence of symptoms. These refinements have been developed in anticipation of early-stage treatment and prevention trials that have already begun in humans. New evidence suggests that partial and sometimes generalized seizures herald AD and can occur even prior to dementia onset.

Eventually, with AD, the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (*anosognosia*), but most remain acutely attuned to their deficits. Changes in environment (travel, relocation, hospitalization) tend to destabilize the patient. Over time patients become lost on walks or while driving. Social graces, routine behavior, and superficial conversation may be surprisingly intact, even into the later stages of the illness.