

THE DIFFERENTIAL DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT

MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is an intermediate or a transitional state between normal ageing and dementia. A simple definition is that MCI patients have more cognitive impairment than one would expect from normal ageing, but their normal daily activities are undisturbed. More specific operational criteria have been developed. MCI is recognized as a risk factor for Alzheimer's Disease (AD), and patients with MCI have an accelerated rate of progression to dementia in general and AD in particular. Although the early descriptions of MCI identified patients with memory deficits ("amnesic MCI"), research has indicated that MCI is not limited to memory, but may also refer to patients with deficits in other or even in several cognitive domains; for example, the executive functions (EXF) and processing speed domains (PS). An expanded concept of MCI is consistent with the fact that measures of memory, complex attention, EXF and information processing speed are the earliest detectable cognitive deficits in patients who ultimately develop dementia.

"Mild cognitive impairment" is an appropriate term to use to refer to many different kinds of patients. It has specific meaning to students of dementia, however, who use it to describe individuals who have more impairment than one would expect simply from normal ageing, but whose general cognitive function and activities of daily living are undisturbed. Such patients do not meet criteria for the diagnosis of Alzheimer's Disease (AD) or any other dementia. But when they are followed longitudinally, they convert to clinical AD at a rate of around 10-15% per year.

The diagnosis of "mild cognitive impairment" is made by administering neuropsychological tests. There is no consensus, however, about how precisely the "condition" should be defined, and minor differences in the defining criteria have resulted in big differences in prevalence and outcome. Many studies indicate that MCI is just an early stage of AD, but not all patients with MCI necessarily progress to overt AD. MCI patients decline at a faster rate than healthy controls who do not have MCI, but less rapidly than the AD patients. MCI patients who possess the apolipoprotein E4 allele are much more likely to convert than patients who do not have the E4 allele.

The concept of MCI has proven to be a useful tool for epidemiological and longitudinal studies of elderly patients. It has also given practicing neurologists a label to pin on a problem that they encounter in increasing numbers in their clinics. But MCI is not a diagnosis; it is not necessarily even presymptomatic dementia. It is a heterogeneous condition. Community surveys find substantial numbers of individuals who meet diagnostic criteria for MCI but do not go on to develop dementia; and others who actually improve or revert to normal. Indeed, it is more appropriate to address the concept of MCI as a symptom complex rather than a discrete diagnostic entity. This being the case, then the identification of a patient with MCI should be the occasion of a differential diagnosis.

Appreciating the heterogeneity of MCI makes sense of widely disparate conversion rates of MCI to AD in community-based and clinic-based surveys, ranging from 4% to 31%. Developing an approach to the differential diagnosis of MCI would make sense to the community neurologist,

who not infrequently encounters a middle-aged or elderly patient in robust good health, but who is cognitively impaired in a specific area, and who may be worried, is this the first sign of AD?

This scenario is unlikely to arise if the only tools at the neurologist's disposal were the Mini-Mental State Exam and the Clock Test. Gross measures like these are hardly suitable for the detection of presymptomatic dementia. But two changes in neurology practice are making the issue of MCI more salient. One is the increased frequency of neuropsychologists allied to neurology practices, and the ready availability of brief neuropsychological screening batteries that can be administered by technicians. The second is the availability of computerized test batteries, like NEUROTRAX® and CNS VITAL SIGNS®.

The wide availability of screening tests that are quick and inexpensive should also be deemed a signal advance, but no new technology is without a downside. (There are Internet sites that will administer an "Alzheimer's Screening Test," too. The results of such tests are not to be trusted, but one will have to deal with patients who have taken them, and are concerned.) Computerized tests are capable of generating large amounts of highly precise and reliable data, and they are highly sensitive to all of the physical and psychological causes of mild cognitive dysfunction. This is what makes them suitable as screening instruments. But tests that are highly sensitive are not necessarily specific and may be given to high rates of false positives.

The problem of non-specificity compounds another problem that is common to all neuropsychological tests, including computerized tests: the problem of "noise." In chapter X (Computerized Neurocognitive Tests) we reviewed the data on the reliability of conventional and computerized neuropsychological tests. The correlation coefficients for the same test administered twice to the same individual are: memory, 0.67 to 0.73; processing speed, 0.78-0.83; and executive function, 0.63-0.74. The correlation of two different tests of the same domain administered to the same individual is: memory, 0.4-0.46; processing speed, 0.5-0.6; executive function, 0.41-0.48. Neuropsychological tests are reliable, but they are also prone to a degree of instability, and different tests can generate different results. That is why "formal" neuropsychological testing usually involves the application of multiple tests of every domain, or at least, of the cognitive domains in which the patient appears to be impaired.

The final problem that is common to every test is the bloke who has to make sense of it. The entry price for mental testing used to be years of special training. Now, psychiatrists, neurologists and psychologists with only passing familiarity with neurocognitive testing can equip themselves with a modern computerized test battery. They have the capacity to measure patients' performance in virtually every cognitive domain, with precision and reliability. How the patient performs on the test is important. What is equally important, however, is how the test is interpreted and what "action steps" the test generates.

Let us presume that the doctor is administering a computerized test battery as a screening measure to every patient over fifty in his clinic. As an extra service, the patient's spouse also is tested. This is what is going to happen: in a substantial number of patients, the test will indicate scores that are "below average" (i.e., 1.5 or 2 standard deviations below an age adjusted mean) in one or more key cognitive domains; for example, in a test of verbal memory, or digit symbol coding (processing speed) or the Stroop test (executive function). This result is sufficient to indicate that the patient has mild cognitive impairment. How, then does one proceed? Is the "diagnosis" of MCI appropriate in such a case? And, if so, what does it mean?

During this discussion, we shall try to alleviate a problem implicit in the term "mild cognitive impairment." When we spell out the phrase with no caps, it means what it says: a degree of cognitive weakness whatever the cause or context; "mild" in the sense that it is present

but not necessarily troublesome, or that it is apparent sometimes but not often or all the time. When we use the acronym MCI, we shall be referring to the clinical condition à la Petersen.

A SYSTEMATIC APPROACH

The author's perspective is from a Neuropsychiatry Clinic, where a staff of neuropsychiatrists and neuropsychologists frequently see older patients who may or may not have complaints of cognitive impairment, but who are discovered to have cognitive deficits when they are tested with a computerized test battery. We routinely use a computerized neurocognitive test battery that we developed ourselves (CNS Vital Signs). Before we had CNS Vital Signs we used the NES2 and MicroCog. We routinely complement computerized testing with conventional testing, and we have the ability to do formal neuropsychological assessments, when they are called for.

We have learned that poor performance on a single test does not mean that a patient is cognitively impaired; that older patients who are cognitively impaired are necessarily developing dementia; and that the discovery of MCI in an older person is not an end in itself but rather the occasion for a differential diagnosis.

From these perspectives, we shall present a scenario: a patient who is more-or-less healthy. A screening test from one of the respectable computerized batteries has identified an area of cognitive weakness. What do you do?

Well, it depends.

It depends on whether this really is a patient, or someone who just happened to take the test to see how they would do. What you do will depend on the age of the patient, what medical conditions they have, and what drugs are they taking. You will behave differently if the patient has subjective symptoms of cognitive weakness, or if family members have noticed anything, or if the patient is having difficulty at work. If there are dementia risk factors, how many does the patient have, and how strong are they. If there is a family history of dementia, how strong is it? Patients with a history of depression are at risk, but patients with late life depression are at special risk. How you proceed depends as much on these external factors as it depends on the results of a screening test.

At any point in the course of the algorithm we shall develop, you have three alternatives. The "default mode" is to shrug your shoulders and advise the patient to come back and take the test again in six months. "Panic mode" is to refer the patient to a specialist. (If you are reading this book, though, you probably *are* a specialist...so change that. "Panic mode" is to order a formal neuropsychological assessment and a full-blown dementia work-up. That is what they are likely to do at the local University Memory Clinic.)

Let us suppose you prefer to take a middle course, and deal with the patient's problem succinctly and efficiently. This is the system we recommend.

AFFIRM THE FINDING

Neuropsychological tests in general, and computerized tests in particular, are very sensitive. There may be a simple explanation for the patient's poor performance. A patient who is fatigued or harried or even momentarily distracted might do poorly on such a test. An older person who is unfamiliar with computers may not understand the test instructions, and many computerized batteries are designed to be administered unsupervised. Maybe the patient

misread the instructions, or advanced the screen before he understood what he was being asked to do.

Repeat the Test

The first thing to do is to repeat the test under optimal circumstances, when the patient is in a better frame of mind, and can focus on the task at hand. Normal performance on repeat testing is reassuring. Persistent deficits need to be explored further.

Give Another Test

Below average performance on a given test, even when the test is administered twice, may be the result of test variability. Give the patient another test, a different test that addresses the same cognitive function. In Table 1, we list a number of cognitive tests that a medical office assistant can administer and score. Armed with these data, one can call a neuropsychologist or another suitably trained specialist as ask for his or her opinion.

TABLE 1. COGNITIVE TESTS SUITABLE FOR A MEDICAL OFFICE

Rey Auditory-Verbal Learning Test
Rey-Osterreith Complex Figure
Verbal Fluency Test
Memory Impairment Screen
Hopkins Verbal Learning Test
Boston Naming Test
Bushcke Selective Reminding Test

Tests of executive function, like Trails or Categories, are good measures of executive function, and coding is a good test of processing speed, but they are better administered by psychologists.

It is not inappropriate to administer the Mini-Mental State Examination (MMSE) in this context. Physicians use the MMSE more than any other instrument to evaluate patients with cognitive disorders. It is quick and easy to administer, and is particularly useful for tracking demented patients over time. Do not, however, expect the MMSE to be as sensitive to MCI as a computerized test battery.

IS THE FINDING MEANINGFUL?

Not every cognitive deficit is potentially pre-dementia. Deficits in tests of memory, processing speed or executive function are more important to pursue; deficits in motor speed, sustained attention, working memory, reaction time, less so.

Mild cognitive deficits are of greater concern when they occur in patients who are well educated and highly intelligent than they are in patients whose native intellectual resources are less robust. Low IQ or poorly educated patients are expected to do less well on neuropsychological tests than their better-endowed peers.

Mild cognitive deficits are, paradoxically, of greater concern in younger patients (50-65) than older patients (>65). One reason is that early-onset dementia follows a more malignant course than late-onset dementia. Also, reversible causes of dementia are more likely to occur in younger patients.

The most common causes of cognitive impairment in middle-aged people are medical conditions, psychiatric disorders, medications and alcohol. (Menopause is often associated with the subjective experience of cognitive impairment, especially in memory, but not necessarily with objective impairment.)

Patients who have had brain injuries, or who have hypertension, diabetes, obesity, or hyperlipidemia, or mood disorders, may do poorly on cognitive tests simply by virtue of their respective condition. The attribution may be correct, but the association is not entirely benign. All of those conditions are dementia risk factors in their own right. By the same token, many commonly prescribed drugs can cause cognitive side effects; but patients with preclinical dementia are much more likely to experience cognitive toxicity.

With ageing, there is a natural decline in all of the cognitive functions. The phenomenon has many names, but we prefer "benign senescence." All things being equal (IQ, SES,

education, health) older patients will always perform less well than younger patients. That is why mental tests are (almost) always standardized for different age groups. So, when a test that has been properly standardized reports that so-and-so is "well below average," the results are scored relative to age-corrected normative data. If a 70 year old has poor memory performance on a test, the results should not be discounted because all 70-year-olds have poor memories. The test results are reported in terms of how other 70-year-olds perform on that test. Or, at least, they should be. That is the problem with the popular Internet tests; psychometricians have not had the opportunity to review their norms and determine if they are sound.

THE DIFFERENTIAL DIAGNOSIS

Now you are at a decision point. Either you are sure that the results of the screening measure are valid and meaningful, or you are not. If you are not sure, you have two choices: repeat the testing in six months' time, or refer the patient to a neuropsychologist.

If you are sure that the patient has an area of cognitive weakness, then that merits clinical attention. But before the patient is subjected to an arduous and expensive dementia workup, one should undertake a differential diagnosis. The cause of the problem may be something less serious than preclinical dementia.

No one's body is perfect, no one's brain is perfect, and no one has a perfect profile of neurocognitive performance. Just about everybody has a relative weakness in one area or another. A mild deficit on a neurocognitive test battery may simply indicate a longstanding and static problem, and not the early signs of mental deterioration. Static cognitive disabilities are either congenital or acquired.

Theoretically, a cognitive impairment that does not change in a six months or a year is static and not indicative of a degenerative process. That is not necessarily true in practice. Dementia is a slow and insidious process, especially at the beginning. Some forms of dementia, like vascular dementia, take a stepwise course, not a gradual decline. Some people who have preclinical dementia try extra hard the next time they take a neurocognitive test. Some actually practice the tests, and I know patients who have cheated. It is an example of "magical thinking": "If I score well on this test, then maybe I don't really have Alzheimer's disease."

If an impairment has the characteristics of a congenital disability, like ADHD or the specific learning disabilities, or of an acquired disability, like traumatic brain injury; and if the impairment is static over 6-12 months, then one might feel secure that early dementia is not at issue.

Congenital Disabilities

The two congenital disabilities of concern are Attention Deficit Hyperactivity Disorder (ADHD or ADD) and the Specific Learning Disabilities (SLD or LD). The prevalence of ADD has been estimated in recent years at between 3-16% of the school age population; 5-10% is a reasonable figure. The prevalence of the specific learning disabilities, including dyslexia, developmental dysphasia, the various nonverbal learning disabilities and apraxias, and impairments in information processing speed is at least as high, although the problems of ascertainment in this area are formidable.

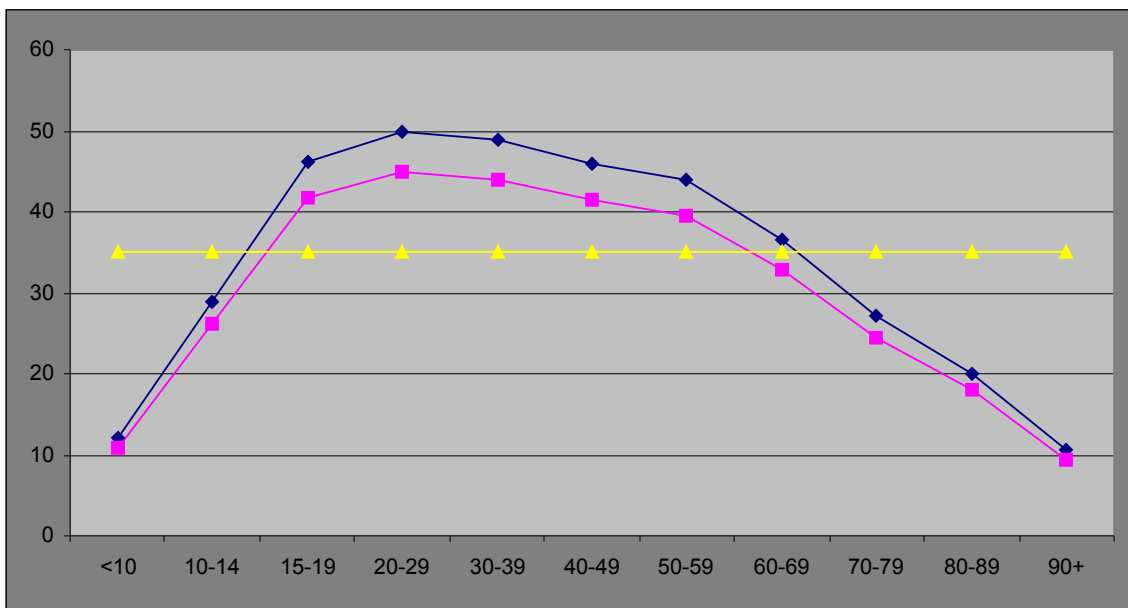
Although many cases of ADHD or SLD are purely developmental and resolve as the patient matures, in the majority of cases the problems persist into adult life. Individuals learn to adjust to the problem, more or less. The most important adaption people make to a learning disability is to choose an occupation that doesn't tax their area of weakness.

A successful adaptation to a disability in learning, memory or attention can be compromised, however, by the negative cognitive changes that accompany ageing. As we have seen, these effects begin during the fifth decade.

Figures 1 and 2 illustrate the impact of a small disability on the consequences of ageing-related cognitive decline. The figures represent data from 1504 normal individuals age 5-96 who took the computerized assessment battery, CNS Vital Signs. The measures are of cognitive flexibility, an EXF score derived from the Stroop and Shifting Attention tests, and of composite memory, derived from tests of verbal and visual memory. In these cognitive domains, performance peaks at age 25-35 and declines gradually thereafter.

Now, consider the consequences of a ten per cent impairment in cognitive flexibility, which would be typical in a population of patients with ADHD, and a similar level of impairment in memory performance, which would typify a population of learning disabled patients. The blue lines represent normals, and the pink lines are the patients with ADHD or LD. The yellow horizontal line represents a theoretical threshold of disability – for the sake of argument, it is the executive ability of a twelve-year old child, or the memory of a five-year old.

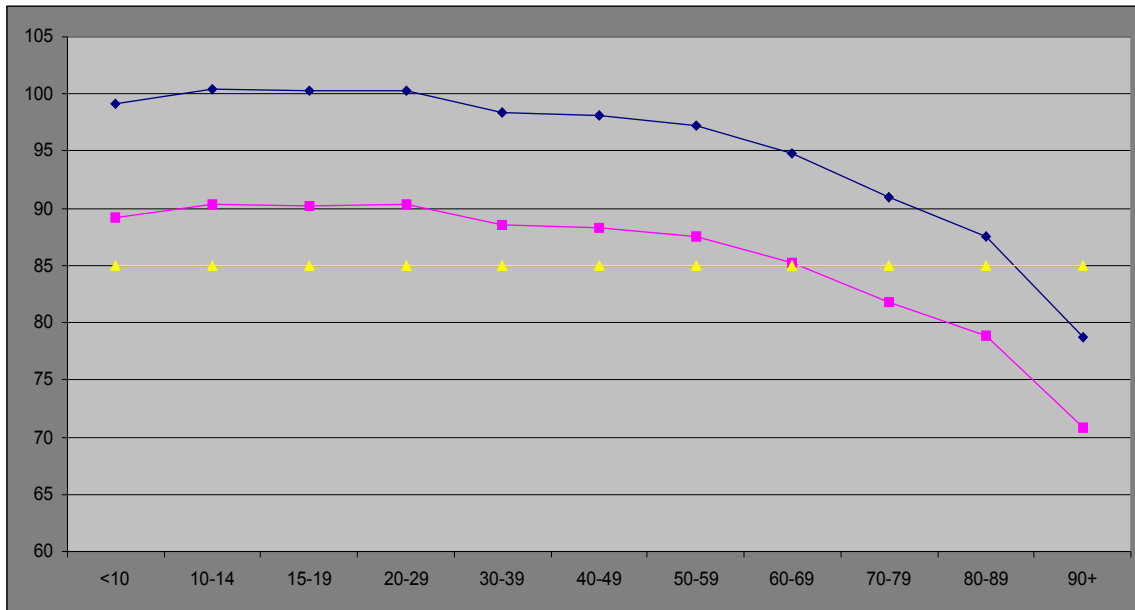
Figure 1. Age-related Change in Cognitive Flexibility, age 5 to 96.



This theoretical population of ADD patients achieves competence in cognitive flexibility as they mature, but later than normal patients do. We have demonstrated this effect in a study of ADD children, adolescents and adults. But as the ADHD patients age, they cross the threshold of disability earlier than normal patients do.

In Figure 2, the LD patients cross the threshold, as they age, earlier than normal patients do. In this model, a ten per cent decrement in memory ability becomes clinically important twenty years earlier.

Figure 2. Age-related Changes in Memory, Age 5 to 96.



This is a schematic version of what happens to ADHD and SLD patients as they mature and as they age, but it demonstrates an important principle. Conditions like ADHD and the SLD have a variable threshold of expression. The threshold is low when the individuals are exposed to highly normative environments, like school, where everyone is expected to master the same subject matter at the same time. The threshold is high during adult life, because people select careers according to their strengths and not their weaknesses. Ageing, however, lowers the threshold again, and a problem that was subclinical for many years may emerge anew as a symptom.

It is odd to think one can make the diagnosis of ADHD or of an SLD in a middle-aged or an elderly person, but we ought to be doing it more often. Forty or fifty years ago, the conditions were rarely diagnosed at all. There was no idea, among professionals, that they were as prevalent as we now know they are. School psychologists were non-existent, and there were no "accommodations" for disabled students. States supported special programs for the blind, the deaf and the mentally retarded, and that was that. The vast majority of children with ADHD or learning disabilities in the 1950's and 60's were never diagnosed. If 10-20% of people, in fact, have ADHD or SLD, a good number of older adults, never previously diagnosed, will present with cognitive symptoms on that basis.

An older adult with ADHD or an SLD can be identified rather easily by asking a few simple questions (Table 2)

Were you an underachiever in school?
Were you hard to manage as a child?
Did you have difficulty with any particular subjects?
Do you like to read? Did you have problems reading as a child?
Were you an underachiever in school?
Were you hard to manage as a child?
Did you have difficulty learning to read?
Did you have difficulty with spelling?
Did you have difficulty with math?
Do you like to read? Did you have problems reading as a child?
Were you ever suspended from school?

The Wender Utah Rating Scale is a well-validated questionnaire that identifies childhood symptoms of ADHD. The diagnosis of ADHD in older adults is more securely made on the basis of the behavioral attributes of the disorder. The most important cognitive deficits of ADHD patients – in attention and executive function – are also typical of some forms of early dementia. Test results by themselves cannot distinguish between ADHD and early dementia.

The cognitive disabilities of learning disabled adults, on the other hand, are rather typical, and are not shared by any of the dementias. Early dementia does not present as a deficit in tests of reading or math. However, LD individuals might have also difficulty on some of the tests that are used to screen for dementia. They might appear to be impaired on tests that require facility with language or reading, like verbal memory or the Stroop test. A patient who had mild dyslexia might do poorly on a prose memory test, a patient with an auditory processing impairment might do poorly on a word learning test, and a patient whose premorbid cognitive weakness was in processing speed or visual-motor performance might do poorly on tests like coding, trails or finger tapping.

The diagnosis of a specific learning disability ordinarily requires the administration of a full psychoeducational battery. This is an expensive and arduous proposition. One can use a screening battery, however, that is less expensive and easier to administer: the vocabulary and matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI), and the reading vocabulary, math calculation and writing mechanics subtests of the Scholastic Aptitude Test for Adults (SATA). A psychological assistant can administer this short battery, and score it, in less than an hour. (An assistant performing these tests ought to be supervised by a psychologist.)

Acquired Disabilities

It is estimated that, every year, more than 2,000,000 Americans suffer a traumatic brain injury. The vast majority, of course, are mild brain injuries, or concussions, and the majority of concussions occur in young, healthy people. One or two concussions in a young healthy person should not cause permanent neurocognitive deficits; the effect of multiple concussions, or of multiple subconcussive blows, is another matter. Severe traumatic brain injuries, of course, can affect every cognitive function, and such injuries are an established risk factor for developing AD. Multiple concussions or subconcussive blows are AD risk factors (“dementia pugilistica”).

The medical history is usually sufficient to establish whether a patient has had a brain injury, or injuries, of any significance. The deficits of a patient who had a severe brain injury are readily apparent in the clinical interview or the neurological examination. Ambiguous situations,

however, may arise: a patient whose brain injury was more than “mild” but less than “severe,” for example. By convention, “moderate” brain injuries are characterized by more than 20 minutes (but less than 24 hours) lost consciousness; they usually result in permanent cognitive deficits that may only be apparent if the patient is tested. Middle-aged patients who have had a severe concussion, or more than one, may also show mild cognitive deficits when they are tested, even years after the event.

The cognitive effects of traumatic brain injuries that are less than severe may be inapparent to the examining physician, and may only be demonstrated by neuropsychological testing. The cognitive domains most commonly affected by moderate brain injuries or by multiple concussions are tests of psychomotor speed (e.g., finger tapping) and processing speed (e.g., digit symbol coding). Tests of memory and executive function may also be compromised, but a cognitive profile that involves impairment in these two areas, but not psychomotor speed, is unlikely to be attributable to an old brain injury. This may be a distinguishing feature

Trauma is only one cause of brain injury. Exposure to environmental toxins, like lead or mercury or carbon monoxide, or to industrial solvents and other toxins, may have subtle effects on cognition. These may never come to clinical attention, until they intersect with ageing-related cognitive decline, and the patient is tested for MCI. The effects of toxic encephalopathy may be seen in any or all cognitive domains, but reaction time and processing speed are primary targets.

Patients with migraine, especially migraine with aura, are at increased risk to show white matter hyperintensities on magnetic resonance imaging. Similar findings occur in asymptomatic subjects. Their nature and long-term consequences are not completely understood, but their infarct-like nature is compelling. White matter lesions in a migraineur may indicate an underlying disease such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), central nervous system vasculitis, or vascular risk factors (antiphospholipid syndrome, genetic prothrombotic factors, oral contraceptives etc).

However, physical changes on neuroimaging have not been clearly correlated with functional impairment in migraineurs. The current literature addressing the neuropsychological consequences of migraine has been far from conclusive, and reports of cognitive testing in adult migraineurs and controls have yielded inconsistent results. Neuropsychological testing suggests that there may be subtle but possibly significant changes in cognition during and between migraine episodes. It has been suggested that migraine patients with aura experience more neuropsychological deficits than migraine patients without aura. There is not compelling evidence, though, that migraine patients have persistent cognitive deficits, relative to normals, or that their cognitive status declines more precipitously with ageing.

Autoimmune vasculitis is usually associated with mild cognitive impairment. Hashimoto's encephalopathy is a rare condition with severe neuropsychiatric and cognitive symptoms that are considered to be fully reversible after a course of steroid treatment. It is not unlikely, though, that at least some patients will have persistent, mild deficits. Systemic lupus erythematosus is associated with impairments in memory, psychomotor speed, and complex attention. In Sjogren's syndrome, executive and attentional deficits have been described. Memory impairment and executive dysfunction have been reported in Behcet's disease. Classic polyarteritis nodosa, the Churg Strauss syndrome and Wegener's granulomatosis may be associated with cognitive changes due to inflammatory encephalopathy. Cranial arteritis belongs among the treatable causes of dementia. In primary angiitis of the CNS, small-vessel disease presents more frequently with encephalopathy. In all of these conditions, the principle is the same. A mild, asymptomatic cognitive deficit can be amplified by ageing.

Viral Encephalitides

HIV enters the CNS early in the course of infection and preferentially affects the subcortical white matter. The early signs of CNS involvement include slowed thinking, abnormal initiation and conceptualization, deficits in complex attention, psychomotor speed, motor coordination, and memory. The development of highly active antiretroviral therapy (HAART) has changed the patterns of HIV related neuropathology and neurological manifestations. The incidence of progressive multifocal leukoencephalopathy (PML) is unchanged, despite HAART, and infections occurring associated with milder immunodeficiency, like toxoplasmosis, varicella-zoster encephalitis (VZVE), or herpes simplex virus encephalitis (HSVE) have become more frequent. Neuropsychological deficits remain common in the HAART era, essentially uninfluenced by HAART. The finding that some neuropsychological functions are improving while other are deteriorating indicates that these deficits do not reflect "burnt out" damage but rather that there is an active intracerebral process occurring, the nature of which is still to be determined.

There is also emerging evidence of mild, but significant neurocognitive impairment in Hepatitis C virus infection, which cannot be attributed to substance abuse, coexistent depression, hepatic encephalopathy or cerebral vasculitis, and which may be related to the detection of HCV genetic sequences in postmortem brain tissue.

Depression

The cognitive deficits associated with depression may be global, or specific. Cognitive deficits specific to depression are the domains of executive ability, processing speed and effortful attention. Because the symptoms of depression and early dementia overlap, distinguishing one from the other has always been central to the evaluation of the elderly patient with cognitive impairment. The distinction is not always easy to make, and for good reason: the two are closely related.

"Late-onset" or "late life" depression (LLD) shares with dementia the cardiovascular risk factors, inflammatory markers and the ApoE4 genotype. LLD is commonly associated with cognitive impairment, which does not usually recede when depression is treated, and patients with LLD are at risk to dementia.

Not every patient who develops LLD will develop dementia; not every case of "pseudodementia" will develop AD. However, the co-occurrence of LLD and cognitive impairment is likely to be an early sign of dementia. The clinical issue, therefore, is not necessarily to distinguish depression from early dementia. That is a distinction without a difference. One might do better to presume that a patient with LLD *cum* cognitive impairment is evidencing an early form of dementia.

If an older patient with mild cognitive dysfunction is depressed, he or she should be treated for the depression. If, with the resolution of depression, his cognitive weaknesses resolve, that is good news, but it not necessarily re-assuring. The cause of the patient's depression should be sought with assiduity. It is a mistake to assume that LLD is the result of psychosocial stressors. That diagnosis should be one of exclusion. The etiology of LLD should be sought first in the patient's *soma*. LLD is strongly associated with medical illness, and that should be investigated aggressively. We have seen patients with LLD and cognitive impairment who had an occult neoplasm.

The second likely etiology is preclinical dementia. The association is sufficiently compelling to warrant a more thorough investigation, and cognitive screening at regular intervals

thereafter. Certainly, one should try to support the patient as he or she deals with the unique psychosocial stressors of ageing. But always remember that stress intolerance is not an inevitable aspect of ageing, but, more often, an early sign of underlying disease.

Drug Effects

Neurocognitive drug effects are a topic in their own right, and deserve a separate chapter (chapter X). With respect to this discussion, patients are more likely to develop medication-related cognitive impairment if they are already weakened by some underlying encephalopathy.

THE PATIENT DOES, IN FACT, HAVE MCI

The patient does, in fact, have an area of cognitive weakness that is reliably demonstrable, and that cannot be attributed to a static, pre-existing condition. The weakness is in a test of memory, processing speed, complex attention or executive function; on one of tests, the patient scores 1.5 SD's below the mean; or two or more domains are impaired at the level of 1.0 SD below the mean. Neither drugs nor depression are at issue. So, the patient has MCI.

At this point, there are two things to do: first, you must commit the patient to serial testing, for example, at six-month intervals. The best way to know whether a condition is progressive is to watch, and see if it progresses. Second, it is appropriate to proceed with an appropriate battery of tests, including a scan, as we shall describe in the next chapter.

The patient has MCI, but what does that mean? Is it pre-dementia, or not? Is it possible to know? At what point does the patient and his family need to start making special plans. Is this the time to begin treatment? And what is appropriate treatment, anyway?

These questions have been addressed, indirectly, in studies of "conversion" from MCI to AD or other forms of dementia. The literature reports a wide range of annual conversion rates, from 4% to 31%. As a general rule, the factors that are most predictive of conversion are also the established risk factors for AD. To wit:

Age: "converters" tend to be older than "non-converters."

ApoE4: the presence of the APOE epsilon 4 allele has been associated with increased risk of conversion, although the sensitivity is rather low.

MCI subtypes: some studies indicate that amnesic MCI (i.e., MCI with memory but no other impairment) is most likely to convert. In other studies, MCI patients with memory plus other cognitive domain deficits, rather than those with pure amnesic MCI, constituted the high-risk group. Patients with "nonamnesic MCI - multiple domains" are thought to be more likely to progress to a non-AD dementia.

Cognitive status: patients who are more impaired on gross measures like the MMSE, the ADAS-Cog, functional activities scales or even a short memory questionnaire are more likely to progress from MCI to dementia. Neuropsychological tests predictive of conversion include letter cancellation (attention), trails (executive function), coding (processing speed), word list learning and prose memory. Studies using cognitive measures generally report good sensitivity and specificity values, although as clinical prediction methods they are imprecise.

Biomarkers: three cerebrospinal fluid biomarkers; total-tau (T-tau), phosphorylated-tau (P-tau) and the 42 amino acid form of beta-amyloid (Abeta42) have been evaluated in numerous scientific papers. These CSF markers have high sensitivity to differentiate early and incipient AD from normal ageing, depression, alcohol dementia and Parkinson's disease, but lower specificity

against other dementias, such as frontotemporal and Lewy body dementia. Abeta42 is usually lower in converters than in people with stable cognitive status and tau protein is higher. An epitope of tau protein (P231) may be more specific for AD and therefore a promising biomarker. In the blood, high beta-amyloid protein levels indicate risk of conversion but only a few studies have been published.

Imaging: Hippocampal or entorhinal atrophy on MRI is one of the most used radiological markers of conversion, although quantification of atrophy is subject to artifacts and anatomic variations. Proton Magnetic Resonance Spectroscopy (MRS) and Positron Emission Tomography (PET) are emerging as promising predictive tools. The highest degree of accuracy (>90%) has been achieved by means of PET plus either memory performance or APOE4 genotype. However, the samples of the published studies are mostly small, and these instruments are not widely available.

Cardiovascular: Most of the cardiovascular risk factors have been connected to conversion. Converters tend to have higher serum high density lipoprotein (HDL) levels, lower serum folate levels, atrial fibrillation and a higher load of white matter lesions on CT or MRI. At least some forms of cerebrovascular dementia are anteceded by a state of MCI.

In fact none of these factors are very strong as dementia predictors, and for every positive result cited above, there is a negative opinion somewhere in the literature. This is only to be expected, given the heterogeneity of patients "diagnosed" with MCI, the arbitrary nature of the cutoff scores, and the wide range of published conversion rates. There are some idiosyncratic findings in the relevant literature. For example, family history of dementia does not usually emerge as a significant predictor, and most of us would find that counter-intuitive, if not dead wrong.

There are a few general principles that emerge, however:

All of risk factors that are established predictors of dementia are also predictive of conversion. Indeed, it would be peculiar were this not so.

We don't know whether the presence of multiple risk factors have an additive or an exponential effect on conversion, but there is good reason to believe that both the number and severity of risk factors contribute to conversion.

The conversion rate will remain ambiguous, and considering the number of factors that have to be considered, clinicians will not be able to make precise predictions with confidence. The large majority of MCI patients, perhaps as many as 90%, will *not* convert within the following year.

And to reiterate what we said before: poor performance on a single test does not mean that a patient is cognitively impaired; older patients who are cognitively impaired are not necessarily developing dementia; and the discovery of MCI in an older person is the occasion for a differential diagnosis.

The relative impact of various risk factors is the way epidemiologists study a problem. Clinicians, on the other hand, use a different method, something that we call "pattern recognition." This is one of those "crystallized" functions that gets better as we get older and acquire more experience. A lifetime of learning enables the experienced physician to process events in a holistic fashion, and to do so efficiently and quickly.

When a clinician suspects AD, it is because the patient is triggering his pattern recognition software. What epidemiologists call risk factors are, to the clinician, components of

the pattern; when they are strong, the pattern comes into better focus. So, this pattern is instantly recognizable: an elderly patient with a typical pattern of memory complaints (from the patient or his family), a positive family history, progressive personality change and loss of interest in one's normal activities, and perhaps a few cardiovascular risk factors.

As computerized neurocognitive testing is more widely applied, patterns that are less well focused will be encountered. We are likelier to have patients who do not experience memory impairment in their day-to-lives, and whose personality changes are mild and indistinguishable from the stereotype of an old gaffer. Physicians will be reliant on cognitive testing as a possible first sign, and this is different from current practice, where cognitive testing is used to affirm one's clinical suspicions.

Whether this will represent an improvement in clinical practice and a benefit to the lives of older people will be dependent on the skills of the clinician who has to interpret the test; how good he is at developing a differential diagnosis; selecting confirmatory tests; and making a treatment decision. We shall address the latter two subjects in the next chapters.