Pre-dementia Diagnosis of Alzheimer’s Disease

Discussed at the 11th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, the Dubois criteria were praised for their potential usefulness in helping improve the ability of physicians to diagnose Alzheimer’s disease (AD) before the onset of dementia with clinical and laboratory tests. However, since their introduction, the criteria have been restricted to clinical research settings as there is still a need to determine their validity in diagnosing patients with probable AD.

By Serge Gauthier, MD, CM, FRCPC; and Antoine Leuzy, BSc

The diagnosis of Alzheimer’s disease (AD) has traditionally required clinical evidence indicating the presence of dementia, defined by a significant decline in two or more cognitive domains with attendant disruption of daily life,¹ followed by a differential diagnosis as to the most likely cause. While the criteria of probable AD² have helped to refine the condition’s diagnosis and promote encouraging developments on the therapeutic front (i.e., randomized trials and cohort studies), the criteria require that dementia be clinically apparent before the diagnosis of AD.

It has also been observed that certain patients reporting cognitive symptoms, typically relating to memory and measurable cognitive decline, transition to AD within two to five years despite not showing functional impairment. Patients with this clinical ensemble are said to suffer from mild cognitive impairment (MCI), a syndrome comprised of a heterogeneous group of conditions, which may be reversible, stable or progressive.³ However, due to its status as a non-specific disorder, regulatory agencies, including the U.S. Food and Drug Administration and Health Canada, are unwilling to approve drugs that would be used to treat MCI, and the diagnosis of this condition does not have specific indications for pharmacologic treatment.

In terms of arresting the progression of AD, the drugs currently under development aim to modify pathophysiologic mechanisms, such as Aβ deposition and tau hyperphosphorylation. To date, such drugs have not proved effective in treating mild-to-moderate stages of AD, which has raised the possibility that such interventions may be effective primarily, if not exclusively, in the earlier, pre-dementia stages of the disease before the prominence of cerebral atrophy.

These considerations have led to the creation of a work group led by Drs. Bruno Dubois and Philip Scheltens, whose 2007 position paper outlined the criteria to help diagnose early AD.⁴

The Dubois Criteria

During the 11th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, held from March 24 to 27, 2010, in Switzerland, the “Dubois criteria,” as they were dubbed by the international community, were praised for their potential usefulness in the pre-dementia diagnosis of AD. The criteria are grouped into two categories: clinical and lab-
The clinical criteria consists of subjective memory complaints, as well as a measurable decline in working memory that remains unimproved despite the assistance of the clinician in the form of cueing. The supportive laboratory criteria consists of brain scans and tests, including magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF) or genetic abnormalities. The introduction of these revised criteria for pre-dementia diagnosis of AD by Drs. Dubois and Scheltens has so far been restricted to clinical research settings. There is still a need to determine their validity and which tests would prove most sensitive as indexed by the patient’s progression and type of dementia. The question of whether more than one test would be required to increase the certainty of this diagnosis remains unanswered.

Following the Publication of the Dubois Criteria

Investigators and regulators alike have recognized that the Dubois criteria offer the possibility of identifying at least one condition from among the many subsumed under the category of MCI that would prove amenable to therapeutic investigation. In addition, some clinicians are better able to treat patients they suspect as having mild AD as it can now be diagnosed prior to the onset of dementia. However, a note of caution was raised about the risk of false positives and of catastrophic reactions in patients with probable AD who are fully aware of the meaning of such a diagnosis. These and other ethical issues regarding early diagnosis of AD have been illustrated in published case studies.

New data suggest CSF abnormalities—specifically lower levels of Aβ42 and higher levels of tau protein—precede changes noted in the Pittsburgh compound-B (PIB)-PET and fluorodeoxyglucose (FDG)-PET, as well as medial-temporal and whole-brain atrophy. Furthermore, medial-temporal atrophy is less specific to AD relative to other laboratory markers. This may require the implementation of a system whereby laboratory findings will possess differential weighting in terms of diagnostic validity. Indeed, some reports suggest that a combination of two abnormal markers carries more weight vis-à-vis the diagnosis of AD. The practicality and consequences of using the Dubois criteria in the absence of established treatment have been examined in the case studies by Frisoni et al.

Some clinicians have already proposed the introduction of modifications to the Dubois criteria to help find subjects with mild memory symptoms and no measurable cognitive decline, yet who present with abnormal laboratory tests specific for AD, including CSF Aβ reduction and/or increased PIB uptake on PET. Once identified, these patients would be invited to participate in preventive clinical trials where reversibility of the biomarkers, as well as the delay of clinical progression, are viewed as equally important. The recent finding that PIB uptake can be reduced by

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**Table 1**

Dubois Criteria Summary

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<th>Clinical Diagnostic Criteria</th>
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<td>Presence of an early and significant episodic memory impairment that includes:</td>
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<td>1. Gradual and progressive change in memory function reported by patients and/or family or friends over a six-month period.</td>
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<td>2. Objective evidence of significantly impaired episodic memory on testing, such as a recall deficit, that does not improve significantly with cueing or recognition testing.</td>
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<td>3. Episodic memory impairment that can be isolated or associated with other cognitive changes.</td>
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<th>Supportive Laboratory Criteria</th>
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<td>The patient presents with abnormalities in one or more of the following:</td>
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<td>1. Medial temporal atrophy on MRI.</td>
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<td>2. Low CSF Aβ42, high tau or phospho-tau levels.</td>
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<td>3. Functional imaging showing reduced glucose metabolism in bilateral temporal parietal regions (FDG-PET) or increased amyloid uptake using amyloid ligands, such as Pittsburgh compound-B (PIB-PET).</td>
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<td>4. Proven AD (presenilin or amyloid precursor protein [APP]) autosomal dominant mutation within the immediate family.</td>
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immunotherapy against Aβ42 suggest that this may be feasible, although most investigators will favor clinical improvement over reversal of laboratory abnormalities as the main treatment goal.5

The Dubois Criteria and AD Research
The ability to diagnose AD in a pre-dementia stage may increase the response to disease-modifying drugs because neuronal cell loss has not yet reached a critical level. Placebo treatment arms can be used until dementia is clinically evident, since there are no proven therapies at that stage of AD. Delaying time to dementia would offer high face validity as an outcome, facilitating acceptance of regulators, payers and users.

The Dubois Criteria and Clinical Practice
At the clinical level, the revised criteria will make it possible to diagnose AD in its earliest stages, an important realization, especially for those in certain professional positions. For instance, physicians, pharmacists, lawyers, and those handling investment portfolios may not be able to make decisions reliably even in the pre-dementia stages of AD. Thus, an early diagnosis of AD would make it possible for an early retirement with full benefits due to a medical disability.

With an increase in self-referrals to our memory clinics from persons at risk of AD—due to a family history of AD, with or without early memory and executive-type symptoms—these criteria offer a framework where a work-up can be made, with attention paid to the risk of catastrophic reaction, which could be preempted using a check-list designed for disclosure of genetic findings, such as ApoE4 carrier status.12

The cost of these additional laboratory tests and related procedures remains to be determined, relative to current standard treatment for AD at the dementia stage. Furthermore, spinal taps are not routinely conducted in Canadian memory clinics, and as such their introduction will require comprehensive and sensitive explanations for patients, as well as the acquisition of new skills on the part of the physician. A central laboratory will likewise have to be established to oversee the analysis of CSF for Aβ and tau protein.

If the number of persons presenting for consultation due to concerns of early AD is high, this will further dilute the already limited human resources (i.e., nurses, neuropsychologists and physicians) currently available to attend to the needs of persons with dementia and their families.

Conclusions
The introduction of the Dubois criteria to help facilitate the diagnosis of AD in the pre-dementia stage marks a turning point in the history of AD therapy, as they will help with a more specific diagnosis of AD than is currently possible with the current clinical criteria and accompanying non-specific laboratory tests. However, the revised criteria require further validation in order to properly determine their positive predictive value. Finally, their widespread adoption will impact the resources currently available for treatment, and as such it is of chief importance that their implementation remain confined to clinical-research settings until existing questions have been answered.

References: