

CLINICOPATHOLOGICAL CORRELATION

Clinical Assessment of Alzheimer's Disease and Response to Donepezil Treatment

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THE CASE

Mr. AB was assessed at the *McGill Centre for Studies in Aging* in December 1995 at the age of 73 for a two year history of decreased recall for recent events and hesitation for words. University educated and active socially, living with his spouse there was some interference of these symptoms with daily life: he had to be reminded of appointments and used the expression "this thing" more and more in his spontaneous language. His medical background was unremarkable and an older brother was a little forgetful.

The neurologic assessment showed a slight difficulty to draw a clock with instructions to put all the numbers and set the time at 11:10. He had no observable impairment of copying a cube. The score on the Mini Mental State Examination (MMSE) (1) was 27/30, well into the normal range.

Uninfused brain computer tomography (CT) imaging showed moderate diffuse brain atrophy evident by widening of the convolutional sulci and mild dilatation of the lateral ventricles.

A diagnosis of dementia caused by Alzheimer's disease (AD) was suspected but follow-up assessments were required for confirmation: six months later his family reported that he repeated questions often, with more hesitation for words leading to angry verbal outbursts; the MMSE score was the same. Nine months after the initial visit the MMSE score dropped to 24/30 and the repeat CT showed increasing atrophy.

A diagnosis of AD was made, and explained to the patient and his family. He was offered to join a

research protocol evaluating the safety and efficacy of Cerebrolysin, a mixture of peptides extracted from pig brain and having demonstrated *in vitro* neurotropic properties. Administered intravenously, the treatment allocation was randomized to placebo or active infusion once a day for 28 days at home. After five months of follow-up, there was no detectable change in clinical status and the MMSE score was 23/30.

The patient elected to start donepezil (Aricept) therapy, a cholinesterase inhibitor acting by enhancing residual acetylcholine activity. Prior to treatment hobbies and interest were listed, including reading of newspapers intermittently and having stopped more complex tasks such as crossword puzzles and playing chess.

After one month on donepezil 5 mg once a day, he described an improved recall for upcoming events, had played and won a chess game against his son (and remembered winning it), and his MMSE score had increased to 28/30. After two months of treatment, there was an apparent loss of clinical benefit, and the MMSE score was 24/30. The dose of donepezil was increased to 10 mg daily. After four months the family reported a decreased in the number of questions repeated, and the MMSE was 25/30. After six months, he is stable clinically. At no time did gastro-intestinal side-effects such as nausea, diarrhea or vomiting occur.

DIFFERENTIAL DIAGNOSIS AND WORK-UP

The diagnosis of dementia requires a decline in memory and at least one other cognitive domain, such as language, interfering with daily life, and representing a decline from a previous level of performance, ruling out delirium and primary psychiatric disorders such as

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major depression (2). Furthermore, the presentation and early course should fit a "typical" profile, i.e., progressive cognitive impairment with no behavioral changes and no motor signs (3).

In the case of highly intelligent and educated individuals, the MMSE may be falsely normal and the clock drawing test (4) is a useful adjunct.

The *Canadian Consensus Conference on the Assessment of Dementia* has recommended a minimum of laboratory work to be performed in patients with typical AD, looking for concomitant and reversible conditions: CBC, serum electrolytes, TSH, glycemia (5).

Anatomical brain imaging using CT usually adds little to the diagnosis of typical AD (6). Magnetic resonance imaging scanning could be useful if a vascular component was suspected based on history of abrupt onset, step-wise progression, history of arterial hypertension or stroke, and lateralized neurological symptoms and signs. Single photon emission tomography may prove useful if a frontal lobe dementia is suspected, demonstrating frontal hypoperfusion. Positron emission tomography is not routinely performed, but would have demonstrated hypometabolism in the associative cortices of the temporal and parietal lobes.

MANAGEMENT

Once the clinical diagnosis of AD has been well established by history, objective mental status assessment, serial observations demonstrating deterioration, and ruling out or treating concomitant illnesses such as depression, it is the physician's responsibility to inform the patient and advise regarding will and advance directives, monitor driving abilities, and discuss realistically the potential advantages of symptomatic drugs available under prescription and others under testing (7).

DISCUSSION

This patient was fortunate to be able to participate in a randomized therapeutic study assessing the safety and efficacy of a neurotropic agent. Still under the blind we do not know if he has been on active treatment or placebo. A recent report has demonstrated that participation in clinical trials, whether on placebo or active drug therapy, has a long term benefit (8). It is the opinion of the AD Society of Canada that patients with AD have the right participate in research (9), with safeguards as to the level of potential benefit and risk at different stages of the disease (10).

The patient then decided to try an established symptomatic drug therapy using donepezil. His therapeutic response was rapid and dramatic, as

reflected by the 5 points improvement on the MMSE score. There was a small, but important to the patient and family, improvement in performance of complex hobbies. He remains autonomous for instrumental and self-care activities after six months of therapy with donepezil, justifying a continuation of treatment beyond the six months duration of pivotal randomized placebo-controlled studies (11). Furthermore, observations of patients on continuous therapy with donepezil demonstrate a stable benefit on cognition up to 38 weeks (12).

It is not known if a structured approach to cognitive training would amplify the effects of pharmacotherapy in AD. Combination of drugs acting on cholinergic synaptic activity could also be of interest, paying attention to additive cholinergic side-effects. Finally, combination of donepezil with agents having a potential stabilization effect on disease progression are logical but require further study (13).

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