

Complex Clinical Conundrums in Psychiatry

From Theory to
Clinical Management

Kuppuswami Shivakumar
Shabbir Amanullah
Editors

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*Dedicated to our parents, wives, and family members
for their continuous support.*

Preface

In today's world of ever-increasing publications, research papers, opinion leaders, and conferences, one is at loss on what to follow in terms of best practice. The treatment recommendations in guidelines do not work for all patients, and the clinician is left with few options to help the patient. While some access web forums and others call a friend at the university, most are unable to access information that is put together in a concise manner to help navigate challenging cases.

The authors who wrote the book, after years of work as clinicians and researchers in different countries, with the aim of giving their patients the best evidence-based care. However, it became abundantly clear that the evidence available often fell short of getting the desired results for patients in our care. To add to this was the ever-increasing number of publications with recommendations that were at times contrary to one another. This book is made up of several chapters written by leading experts from across the globe, covering a range of topics from conditions in adolescence to those in the elderly.

This book seeks to bridge the gap between theory and clinical application with a view to help clinicians use a combination of evidence, experience, and practical solutions. While the authors advise that one follows the existing guidelines to the best of the clinician's ability, this book offers options based on the experience of the authors from diverse backgrounds with a common interest in patient well being. There are certain conditions where treatment resistance poses a unique challenge and will require the readers to look at emerging best practice and experience; moreover, it is always important to include the patient and where possible the family in decision making.

We are delighted at the support we got from various authors across the globe; despite their busy clinical schedules, they stuck to our deadlines and our comments. We are also grateful to our mentors, colleagues, and graduate students for their editorial support.

Nadina Persaud and her team at Springer have been supportive beyond the call of duty. Thanks to all of them. Finally, there are those who may not respond to the treatments we propose, but this subgroup of nonresponders is the reason for medicine advances. We owe it to them to try our best. We hope you enjoy this book and that it benefits those who need it the most.

Sudbury, ON, Canada
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April 2018

K. Shivakumar
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A Complex Case of Major Neurocognitive Disorder: Alzheimer's Disease

1

Popuri M. Krishna, Kuppuswami Shivakumar,
and Shabbir Amanullah

Abbreviations

Aβ42	42-amino acid beta-amyloid
AD	Alzheimer's disease
ADLs	Activities of daily living
APOE	Apolipoprotein E
APP	Amyloid precursor protein
CSF	Cerebrospinal fluid
CT	Computed tomography
DSM	Diagnostic and Statistical Manual
MAPT	Microtubule-associated protein tau
MCI	Minimal cognitive impairment
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
NP	Neuritic plaques
PIB	Pittsburgh compound B
PSEN	Presenilin
SPECT	Single photon emission computed tomography

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Major Neurocognitive Disorder (MND) is a term that has been incorporated in DSM-5 to replace the term dementia. MND is a clinical syndrome characterized by global cognitive decline from the previous level of functioning as evidenced in loss of one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptomotor or social cognition). Occurring in clear sensorium, this decline interferes with the individual's ability to be independent. MND is a public health issue with significant impact on patients, their families, and the community. Dementia is already an epidemic in developed countries (Murray and Lopez 1997). In more than 50% of cases of Major Neurocognitive Disorders, Alzheimer's disease is the cause (Alzheimer's Association, 2011). The pathology of AD is clearly defined to consist of Neuritic Plaques (NP), Neurofibrillary Tangles (NFT) and subsequent neuronal loss, which is present in a typical distribution in the brains of the afflicted patients. The two most common risk factors for AD are advanced age and family history of dementia.

1.1 Case History

A 52-year-old married female presented with her husband for a geriatric assessment, with concerns about her memory. Over the previous 3 years, her

husband noticed that she was repeating the same question, having forgotten that she had asked the same question a number of times previously. This repetition has increased in intensity while waiting for this consult. In the months before the assessment, she started forgetting events. She started misplacing things around the house. In one instance, she forgot where she parked the car and required her husband's help. She frequently forgot her appointments. She did not have any word finding difficulty and was able to recognize people without difficulty. She continued to drive to work, and there were no reports of her losing her way around. She seemed to be more forgetful when she was nervous. She was attending to all her activities of daily living (ADLs). She maintained meaningful employment in the family business – a local shoe store. She was able to handle the customers and the cash register. She did not have any mood changes nor experience incontinence.

Her medical history was positive for lupus, diagnosed about 4 years ago. She also had non-ulcerative dyspepsia. There was no history of diabetes, hypertension, or hypercholesterolemia. She was taking hydroxychloroquine 200 mg P.O. daily. There were no allergies to medication. Her maternal grandmother had a history of Alzheimer's disease at a later age. Her mother died of cancer at 65. Her premorbid personality indicated an outgoing, happy, and jovial person of average intelligence. She liked to sing while at home. She liked cooking and baking.

In her personal history, there is evidence of physical, emotional, and sexual abuse by family members. She completed grade 8 education and later worked as a waitress after moving out of her family home. She got married at 21 and had three children. There is no history of alcohol or substance abuse.

Her physical and neurological examinations were within normal limits. She scored 21/30 on MMSE, but otherwise her mental state examination was normal.

Her CT scan and hematological exam were within normal limits. Her B12 was 229 picograms/ml, TSH 1.10 milli-IU/ L. She was diag-

nosed as having Major Neurocognitive Disorder-Alzheimer's Disease. Given the early age of onset, she was referred for further testing for confirmation of diagnosis.

1.2 Genetic Factors Contributing to the Onset of Alzheimer's Disease (AD)

Between 50% and 70% of patients with MND are diagnosed to have the Alzheimer's disease (AD) subtype [26]. A major risk factor for AD is genetic, with 70–80% of cases being hereditary. This is supported by twin studies [7]. AD is a heterogeneous condition involving the interaction of genetic, environmental, and personal factors. Given that the etiology is polygenetic, a predominance of certain gene types may increase the risk of AD, while some genes may be protective [5]. The most well-known gene is the APOE gene. The $\epsilon 4$ allele of APOE gene is a risk factor for AD. Heterozygous $\epsilon 4$ carriers have three times, and homozygous carriers have 15 times the risk of non- $\epsilon 4$ carriers. The APOE $\epsilon 4$ gene is probably involved in the age of onset of the AD [8]. The APOE gene has low penetrance, thus implicating the involvement of other genes involved in the phenotypic expression of AD.

There are two types of expression of AD, familial and sporadic. Among the familial expression, there are two patterns: early-onset and late-onset familial patterns. Late-onset familial AD is the more common form, which is seen in individuals over age 65. Genetic risk decreases with advancing age in some studies [30]. Late-onset familial AD is mediated through several susceptibility genes, including APOE. There are three allelic variations of APOE: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 2$ allele is relatively rare and may provide protection against the onset of AD. The $\epsilon 3$ allele is most common in the western European population and may be neutral in its effect. However, those individuals who are homozygous for the APOE $\epsilon 4$ allele have the much higher burden of amyloid plaque than those with other genotypes [13].

1.3 Genetic Factors Involved in the Early Onset of Alzheimer’s Disease

About 30–40% of early-onset MND-AD has been shown to be due to familial autosomal inheritance pattern. Other genes are probably involved as risk factors (Table 1.1).

The autosomal dominant inheritance pattern of genes shows high penetrance with more severe neuropathological changes. It is also found that the age of onset in these individuals is in the range of 30–50 years. All the genetic forms of MND-AD result in overproduction of the Aβ42 amyloid peptide. The extra chromosome 21 in Down’s syndrome with an additional APP gene accelerates the onset of AD by about 30 years earlier than in patients without an extra chromosome 21. PSEN-I mutations are by far the most common gene involved in early-onset AD. The PSEN-II gene is less common and is seen most often in those of German descent living in North America. As noted before, the APOE ε4 gene probably modifies the age of onset of AD by uncertain molecular mechanisms [8]. Other genes may be involved, but their relationship to AD susceptibility or protection is not yet clearly understood (Table 1.2).

1.4 Pathological Effects of the Genetic Factors in an Alzheimer’s Disease

The genetic effect of various genes in the pathological process of producing the neurodegenerative changes seen in MND-AD is unclear. The

Table 1.1 Genes implicated in early-onset AD [5]

Protein	Chromosome	Inheritance pattern
Amyloid precursor	21	Autosomal dominant
Presenilin I	14	Autosomal dominant
Presenilin II	1	Autosomal dominant
APOE	19	Risk factor

Table 1.2 Other genes with possible implications in early-onset AD [5]

ACE	MTHFR
CHRNA2	NCSTN
CST3	PRNP
ESRI	GAPDHS
TF	IDE
TFAM	TNF

most common histological changes seen in MND-AD are neuritic plaques (NP) and neurofibrillary tangles (NFT). Other less conspicuous findings are granulovacuolar degeneration, Hirano bodies, and amyloid angiopathy. The neuritic plaques primarily contain amyloid proteins, particularly the Aβ42 peptide in patients with MND-AD. Those individuals who are homozygous for APOE ε4 allele have much higher plaque burden than those who do not. This suggests a pathological effect of APP in persons with MND-AD. APP is cleaved by three secretases: alpha, beta, and gamma. Mutations in PSEN genes lead to an alteration in gamma-secretase, generating higher loads of Aβ42. One hypothesis is that Aβ42 induces an inflammatory response in the brains of patients with MND-AD and promotes oxidative injury to the neurons. The deposit of amyloid in NP may be fairly extensive by the time early symptoms of MND-AD appear [24].

NP are found in the posterior neocortex, especially in the temporal and parietal regions of the brain and, less abundantly, in the frontal regions [2]. Diffuse plaques containing Aβ2 peptide are common in brains without cognitive impairments. In patients with dementia, there is a negligible correlation between NP counts and the degree of cognitive impairment. NP burden does not change even in the progression of symptoms. This is shown by PIB PET imaging studies, where amyloid burden reaches the maximum by the time patients reach the minimal cognitive impairment (MCI) stage in MND-AD.

NFT are primarily intraneuronal. The burden of NFT is better correlated with disease severity than NP count [6]. The NFT formation and neu-

ronal damage progress during MND-AD. The neurotransmitter changes primarily in acetylcholine and other neurotransmitters such as dopamine, serotonin, norepinephrine, and glutamine occur as epiphenomenon due to the disruption of neural pathways. In combination with the inflammatory processes, this leads to neuronal death and disconnections between the neurons by disrupting the dendrites and axons. These changes lead to the cognitive, behavioral, and psychological symptoms in the MND-AD.

NFT are primarily composed of microtubule-associated proteins, tau MAPT [15]. In MND-AD, the tau is excessively phosphorylated. This excessively phosphorylated tau cannot be degraded by the neurons, and it accumulates in the neurons. The genes for different isoforms of tau are located on chromosome 17. It is not clear what induces the hyper-phosphorylation of tau. It is suggested that A β 42 peptide may induce this process. NFT are initially seen around middle age, starting in the transentorhinal area of the brain [6], and then it progresses to entorhinal and hippocampal (CAI) regions. Finally, this progresses to other neocortical association areas. Increased brain volume loss is correlated with the involvement of neocortical regions by NFT.

The hippocampal and medial temporal areas affected are consistent with early anterograde amnesic symptoms in the initial stages of MND-AD. Amyloid angiopathy is commonly found in the brain in patients with MND-AD [14]. However, the presence of amyloid angiopathy does not appear to have a clinical correlate. Other age-related changes in the brain also have a cumulative effect on the pathology of MND-AD.

Loss of memory occurs fairly early with the development of agnosia, apraxia, and aphasia. Patients have gradual deterioration of their functional abilities in the middle stage. In the terminal stages, problems develop with mobility and continence. With good health and good care, patients with MND-AD may live a long time, even in near-vegetative states. Death usually occurs due

to frailty resulting from intercurrent infection or other medical causes.

1.5 Continuation of the Case

Four years later, the patient's husband brought her back to the emergency department of the local hospital. Her memory had worsened to the point that she was unable to take care of herself. Her husband and her daughters were providing care along with the support of community services. She was unable to attend to her activities of daily living (ADLs). She had difficulty recognizing familiar people in her life, including her family members. She had difficulty maintaining her sleep. She lost her appetite and dropped 6 pounds in weight. She was often irritable in her mood. Her speech was reduced to simple words, spoken out of context. She was unable to communicate her thoughts coherently. Later, she stopped communicating with her family. Occasionally, she was incontinent of urine.

Over the last 4 years, she was assessed at the tertiary care hospital. She underwent neuropsychological testing after her clinical assessment. Based on the discrepancy of her neuropsychological test scores for her age and the history of sexual abuse, she was diagnosed to have conversion disorder with amnesic symptoms. She was recommended to have psychological counseling and started on a trial of sertraline medication. She was advised to follow up with her primary care physician.

In spite of these interventions, her memory and capacity to function continued to deteriorate. The family was concerned for her safety. They could not leave her at home as she could not live unsupervised. She was deemed incompetent 1 year ago for both personal care and finances, and her husband was appointed substitute decision-maker.

A CT scan and hematological exam done at the second presentation were reported to be normal. She was admitted to the psychiatry unit for further assessment and care planning. A SPECT

scan and EEG were performed along with cognitive and functional assessments. The SPECT scan showed a surprisingly abnormal scan for her age of 57 years. She had worse uptake in parietal areas in comparison to the frontal areas. There were decreased uptake in temporal areas, more so on the left side, and only mild decreased uptake in occipital areas. There was a normal uptake in the basal ganglia. Her EEG was abnormal, with slow background activity. There was a persistent mixture of delta and theta wave activity. These findings were consistent with advanced Alzheimer's disease. Her MMSE was 3/30, compared to 21/30 4 years earlier. She showed severe functional impairment. She needed assistance with her ADLs. She was diagnosed to have a major neurocognitive disorder of early-onset Alzheimer's disease, moderate in severity. She was started on galantamine 4 mg P.O. twice daily, gradually to be increased up to a maximum of 24 mg daily. Her antidepressant medication was stopped. Her husband wanted to provide care at home with community supports. Thus, she was discharged back to her home.

1.6 Natural History of Alzheimer's Disease?

It has been shown that the pathological process of MND-AD begins several years before the onset of clinical and functional changes of the individuals with MND-AD [3]. It is possible to have imaging studies for amyloid deposition by Pittsburgh compound B (PIB), PET, and SPECT studies [21]. The natural history of Alzheimer's dementia has been well-described. Time from diagnosis to death in the tertiary centers is on the order of 10–12 years. The median time from onset of symptoms to death is around 3–5 years [20]. Most patients exhibit slow progression. In Cache County Study, a quarter of the patients showed limited progression from milder stages of MND-AD, even after 3–5 years of onset [18]. The presence of psychosis and extrapyramidal symptoms is associated with faster progression, along with the presence of

hypertension, diabetes, hyperlipidemia, and atrial fibrillation.

1.7 Investigations Used to Establish the Diagnosis?

After completing a comprehensive history and physical exam, most cases of MND-AD are diagnosed clinically. Obtaining baseline labs and electrocardiograms is the first step in the investigation. Less than 1% of the dementias are truly reversible, even with intervention. Less than 10% of patients with dementia may show a reversible cause by the laboratory investigations [11]. Additional lab evaluation workup can be done if other risk factors are identified in the patient's history. Lumbar puncture (LP) and electroencephalograph (EEG) are done in patients where diagnosis is unclear. The American Academy of Neurology recommends either computed tomography (CT) or magnetic resonance imaging (MRI) [19]. Other methods of assessment include PET, SPECT, genetic testing, and brain biopsy. Some examples are given below (Figs. 1.1, 1.2, and 1.3).

MND-AD like the case presented: typical posterior temporoparietal predominant hypometabolism with hypometabolism more prominent in the left hemisphere and lesser involvement of the frontal lobes. Behavioral bifrontal (could be asymmetric) predominant FTD with little or no posterior temporoparietal hypometabolism.

F18-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with autopsy-confirmed Alzheimer's disease (AD, rows 3 and 4) frontotemporal degeneration with ubiquitin inclusions (FTD, rows 5 and 6). Scan data are displayed using three-dimensional stereotactic surface projection (3D-SSP) maps from six perspectives, illustrated in a reference image of the brain surface (row 1). These reference images show regions of the brain typically most affected in AD in shades of orange and most affected in FTD in blue, purple, and aqua. Local cerebral metabolic rates for glucose (LCMRGlc) relative to the pons are displayed

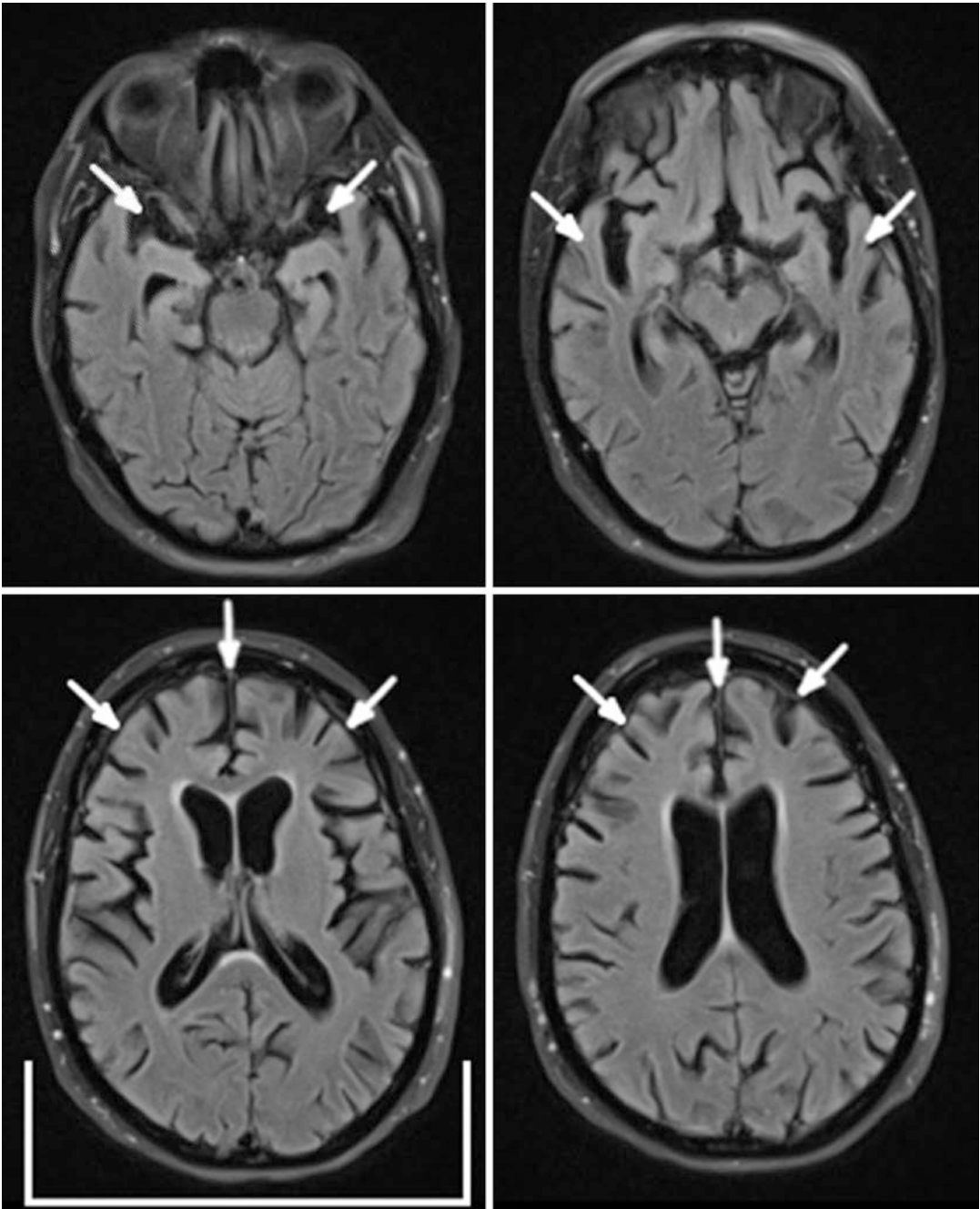
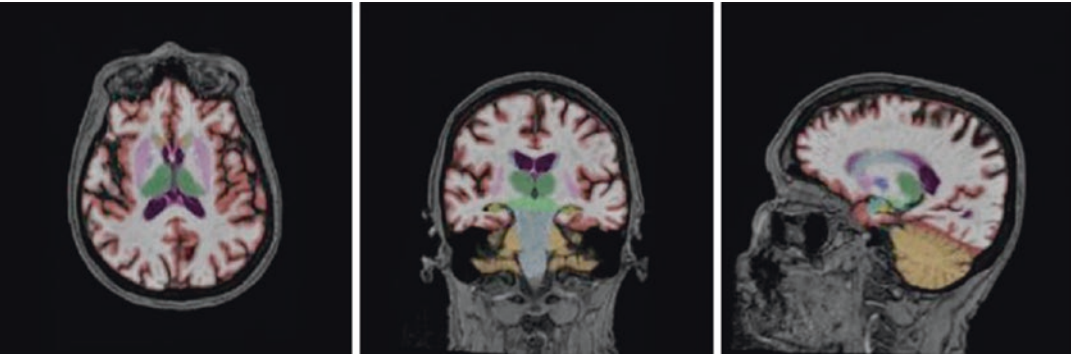


Fig. 1.1 Typical brain magnetic resonance imaging (MRI) findings in a patient with autopsy-confirmed frontotemporal degeneration with TDP-43-positive inclusions. The MRI obtained when the patient had only mild symptoms shows the characteristic focal pattern of atrophy (arrows). There is symmetric widening of sulci and

shrinkage of gyri in the anterior temporal regions (top row) and in the bilateral frontal cortex (bottom row). These regional changes are easy to overlook and best recognized when compared in the same scan with the size of sulci in posterior regions of the cerebral cortex (bracket)

MORPHOMETRY RESULTS



Hippocampal Occupancy Score (HOC)		0.62	
Brain Structure	Volume (cm ³)	% of ICV (5%-95% Normative Percentile)	Normative Percentile
Hippocampi	5.00	0.31 (0.38-0.52)	< 1
Lateral Ventricles	30.03	1.84 (1.09-3.87)	40
Inferior Lateral Ventricles	3.09	0.19 (0.08-0.21)	91

AGE-MATCHED REFERENCE CHARTS

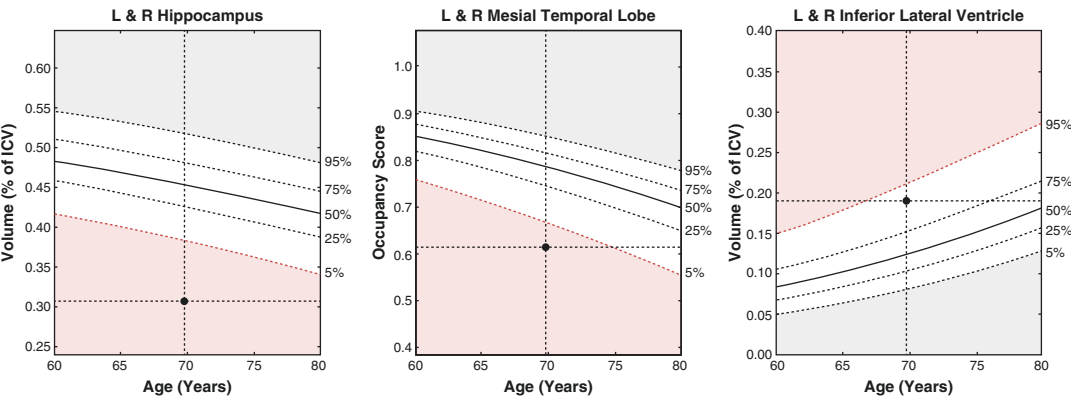


Fig. 1.2 Typical MND-AD qMRI NeuroQuant and MRI selection of horizontal slices – CACIR 06379. Illustrate selective hippocampal atrophy in MND-AD (Figure pro-

vided Courtesy of Norman L. Foster, MD; Richard D. King, MD, PhD; and Yao He, Center for Alzheimer’s Care, Imaging and Research, University of Utah)

using a color scale shown below the images with the hotter colors representing higher rates of glucose metabolism (rows 2, 3, and 5). Statistical maps also can be constructed with z-scores of metabolic rates for each patient (rows 4 and 6) compared to 27 cognitively normal elderly individuals (row 2) using the same color scale. The patient with AD had symptoms similar to the case presented in the text and shows typical posterior temporoparietal hypometabolism, with hypometabolism more prominent in the left hemisphere corresponding to the patient’s prominent language deficits, whereas a patient with FTD with behavioral symptoms

shows bifrontal and left anterior temporal predominant hypometabolism (Fig. 1.4)

Amyloid PET imaging of Alzheimer’s disease neuritic plaque pathology with AV-45 (florbetapir) in two elderly individuals with dementia in the Alzheimer’s Disease Neuroimaging Initiative (ADNI). Scan data are displayed using 3D–SSP as in Fig. 1.4. Semiquantitative values of tracer binding in the brain surface relative to the cerebellum are shown in standard uptake value ratios (SUVr). Average values in 168 ADNI elderly control subjects (row 2) only show expected non-specific binding in white matter tracts in the brainstem and corpus callosum. This same pat-

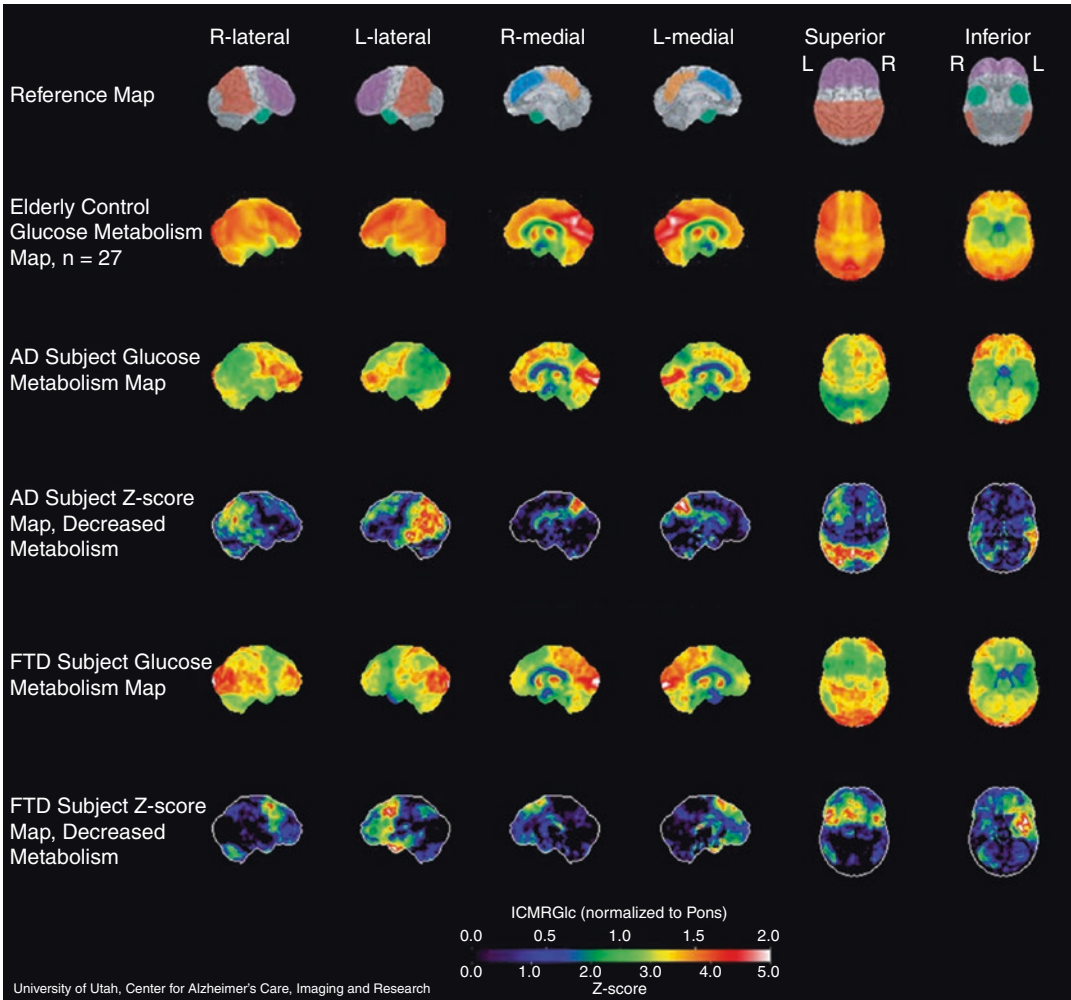


Fig. 1.3 FDG-PET: typical single-case stereotactic surface projection image presentation

tern is seen in the patient in row 3, who has a negative scan. The patient in row 4 shows the typical diffuse pattern of increased binding seen in Alzheimer's disease dementia. In this patient, the visual cortex is the only cerebral cortical region spared. Note that the distribution of amyloid plaque is not limited to regions of the brain that are typically hypometabolic on FDG-PET and that binding is minimal in the cerebellum of all cases, including those with Alzheimer's disease dementia (Fig. 1.1).

(Figure) provided Courtesy of Norman L. Foster, MD; Richard D. King, MD, PhD; and Yao He, Center for Alzheimer's Care, Imaging and Research, University of Utah).

1.8 Making a Diagnosis of MND-AD

In general, making a diagnosis of MND is a two-step process. In the first step, determine if there is a dementia process. Second, proceed with the inquiry of the type of MND. The most common clinical conditions to be ruled out are cognitive changes due to depression or chronic delirium. Secondary medical conditions such as normal pressure hydrocephalus (a triad of dementia, ataxia, and urinary incontinence) and hypothyroidism should be ruled out. Confirm if the criteria for MND are fulfilled (Table 1.3 and 1.4)

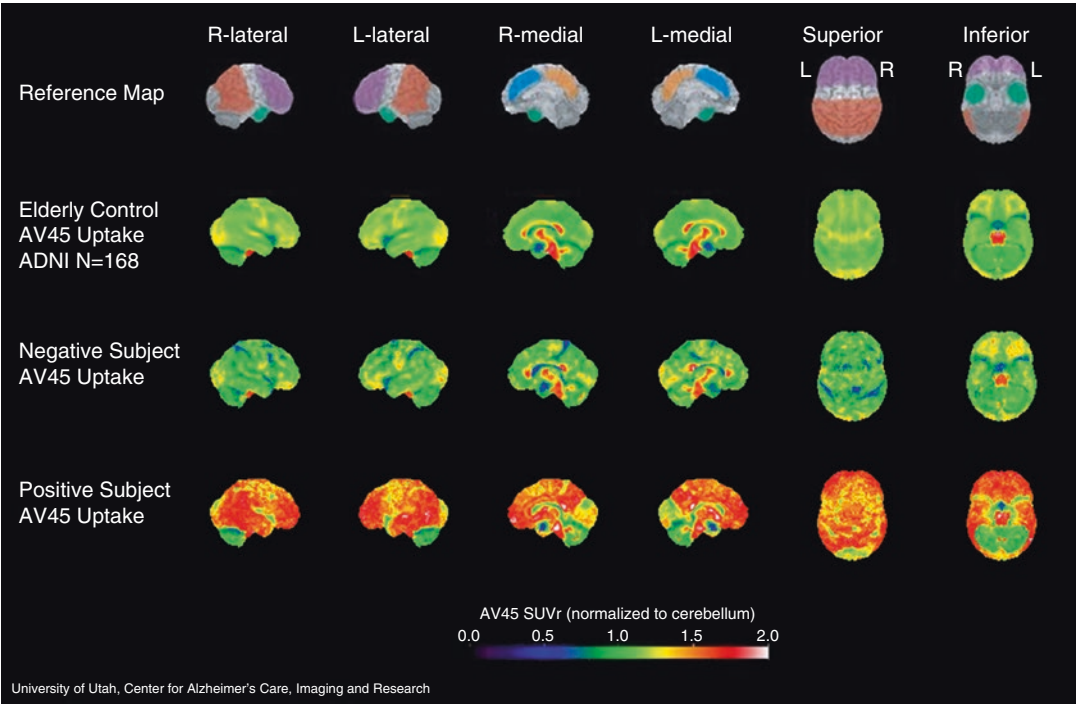


Fig. 1.4 Positive AV-45 amyloid case typical single-case SSP image (Figure provided Courtesy of Norman L. Foster, MD; Richard D. King, MD, PhD; and Yao He, Center for Alzheimer’s Care, Imaging and Research, University of Utah)

Table 1.3 Cognitive domains and relevant neuropsychological tests

Cognitive domain	Neuropsychological test
Complex attention	Trail Making Test A, Digit Span
Learning and memory	California Learning and Memory Wechsler’s Memory Scale
Perceptual motor	Finger-tapping test
Language	Boston Naming, verbal fluency
Executive function	Wisconsin Card Sorting, Trail Making Test B
Social cognition	Thematic Apperception Test

Table 1.4 Differences between mild neurocognitive disorder, major neurocognitive disorder, and major neurocognitive disorder due to Alzheimer’s disease

Mild neurocognitive disorder	Major neurocognitive disorder	Major neurocognitive disorder due to Alzheimer’s disease
Modest decline in one or more cognitive domains	Significant decline in 1 or > cognitive domains	Significant decline in 1 or > cognitive domains
Person is concerned of the change	Usually, family are concerned of the change	Usually, family are concerned of the change
Cognitive deficits do not interfere with ADL or IADLs	Significant interference of ADL or IADLs	Significant interference of ADL or IADLs
Cognitive deficits are not due to delirium or other mental disorders	Cognitive deficits are not due to delirium or other mental disorders	Cognitive deficits are not due to delirium or other mental disorders
Progression is variable 5–10% may convert to Alzheimer’s disease	Variable depending on the type	Insidious onset and gradual progression over years

Most cases of MND are due to Alzheimer's disease. The next most common cause is a mixture of vascular and Alzheimer's disease (reference for epidemiological studies latest). Vascular dementia and DLB are the next most common causes. FTD is more common in earlier ages of onset (30–64 years) and decreases as age advances. It is rarely seen after 70 years of age. In one community study in the UK [27], frontotemporal dementia (FTD) was 15.7% and Alzheimer's dementia (AD) was 25% in people with dementia between the ages of 30 and 64 years.

With available clinical investigations, the Alzheimer's dementia is classified as probable, possible, and definite.

According to McKhann's criteria, the diagnostic certainty of AD has three levels: definite, probable, and possible. A definite diagnosis can only be done by brain biopsy. A probable diagnosis is done when the dementia syndrome has insidious onset and gradual progression, with cognitive deficits in multiple domains and at least basic cognitive testing (MMSE). When these criteria are not completely met (e.g., a fluctuating course, sudden onset), then a diagnosis of possible AD should be made [23].

About a week later, the patient was brought back to the hospital as she was becoming more aggressive with family members. The family was unable to manage her at home. Her husband was not able to sleep and was feeling helpless. She was admitted to the medical unit to rule out acute medical conditions and to make an appropriate care plan. Galantamine, which had been initiated earlier, was continued.

In the hospital, she was started on (SSRIs) escitalopram 10 mg P.O. daily along with risperidone, 0.25 mg twice daily. Her medical investigations were negative. Her agitation increased, and she was given frequent doses of haloperidol for management of her agitation. Three weeks later, she was noted to be walking around naked and sexually disinhibited in the hospital. She also had decreased sleep and was found to talk loudly when awake. She was euphoric in her mood. She was wandering into other patients' rooms. Occasionally, she was irri-

table and impulsive in her behavior. She was noted to be talking to herself. The nursing staff was unable to redirect her behavior. She needed assistance with all her ADL care.

Her risperidone was gradually increased and escitalopram was discontinued; memantine was added with the family consent, and they visited often. They declined genetic testing for the patient owing to cost. Her daughters also refused genetic testing for themselves. The poor prognosis was discussed with the family. There were no advanced directives from the patient. The family decided to keep her comfortable and safe, agreeing to long-term care in a supported environment.

1.9 The Cognitive and Behavioral Symptoms in MND-AD

The central feature of Alzheimer's disease is the gradual progression of multiple neurocognitive dysfunctions, initially starting as difficulties in new learning and recent memory. Amnesic patients often repeat themselves in conversation, ask the same question repeatedly, or forget recent conversations. Family members often ignore symptoms as these are misinterpreted as "normal aging." Symptoms are typically present before family members bring the patient for medical attention. The loss of ability to carry on activities such as shopping, driving, handling money, or doing chores around the house is more frequently the reasons than forgetfulness for such presentations. Sometimes getting lost while driving or accidents while driving may bring the patient medical attention. Neuropsychiatric symptoms are more likely to bring the patient for evaluation than forgetfulness.

Deficits in frontal executive function are noted in the difficulty in planning the meal for dinner, organizing the kitchen, or following a recipe. Other changes include difficulty in recognition of people (agnosia), difficulty in cutting the vegetables or difficulty in dressing (apraxia), and difficulty in naming or finding the right word to speak (aphasia). Other cognitive

deficits include difficulties in reading (dyslexia) or writing (dysgraphia) and difficulties in doing simple calculations (acalculia). In moderate to severe stages, patients may have right/left disorientation.

Behavioral symptoms are often due to delusions, hallucinations, or mood changes. Common mood changes are anxiety, depression, irritability, anger, and elation. Other behavioral symptoms are apathy, hyperactivity, and aggression. Sometimes the behavioral changes occur due to the personality changes.

In some patients, changes in biological functions such as sleeping, eating, and sexual disinhibition occur in all stages of AD. Other physical symptoms such as swallowing, continence, and gait difficulties occur as the disease progresses.

As the dementia progresses, difficulties in day-to-day functioning and behavioral symptoms become more common. Misidentification syndromes occur commonly. The patient may complain that someone else has been in the house. Sometimes they identify the family members as someone else in the disguise of other family members (Capgras syndrome). Sometimes they misidentify their own image in the mirror as someone else.

1.10 General Principles of Management of a Patient with Alzheimer's Disease

Management of Alzheimer's disease follows the general four pillars of dementia care. The first pillar is to modify the aspect of the disease. Only a few therapies such as choline esterase inhibitors are available at this time. The approved medications are donepezil, rivastigmine, and galantamine. The second pillar is to manage the symptoms of AD. These are the cognitive, neuropsychiatric, and functional symptoms.

The third pillar is to provide supportive care for the patient with AD. The final and fourth pillar is to support the caregivers for the dementia care. These interventions should be evidence-based approaches.

1.11 Effects of MND-AD on the Family Caregivers

Prolonged activity of providing care for a family member with Alzheimer's disease will frequently lead to chronic stress in one or several members of that family. The caregiver's burden is the subjective perception of that burden of providing care. This stress may interfere with physical, social, emotional, and financial functioning of the family care providers. Several scales can subjectively or objectively measure the caregiver's burden. The Caregiver Self-Assessment Questionnaire is a 16-item scale that can be answered yes/no. This can be used in an office setting for rapid screening of caregiver burden. Anxiety and depressive symptoms are common, while some families express pride in providing care for their loved ones. Successful family caregivers are flexible in adjusting the expectations of themselves and the older adult. The primary caregiver at home needs occasional breaks, respite, backup, and services to support them [12].

Sometimes interpersonal difficulties arise when siblings attempt to divide the responsibilities of caregivers. Families face the realities of loss and grief during the process of caregiving. Sleep quality can be affected significantly in caregivers. The Pittsburgh Sleep Quality Index can measure this more reliably [10]. Primary care physicians must be aware of these factors in the family when they are planning the care for MND-AD patients. Physical symptoms such as hypertension, diabetes, and coronary artery diseases are also higher in the family care providers than the general population [29]. Premature death is associated with spousal caregiver strain [28].

1.12 Legal and Ethical Encounters when Managing a Patient with MND-AD

As the major neurocognitive disorder of MND-AD has a prolonged course of 8–10 years, families face various legal and ethical issues during its course. Retrospectively, in the early stages

after the diagnosis, the family is better served when an open discussion occurs with the family members, including the patient and their primary care physician [9]. Advanced directives are sought and recorded by the family members. Prior wishes of the patient are respected throughout the course of MND-AD. It is wise for the family to discuss the patient's wishes in a sensitive manner. This discussion may include end-of-life issues as well.

Capacity assessment in regard to driving will be encountered in moderate stages of MND-AD. Given the possibility that the patient may lose their ability to take reasonable decisions toward their personal treatment, care choices, and ability to manage her finances, a power of attorney might be chosen by the patient. Ideally, such advanced directives and the power of attorney papers are kept with the patient's lawyer and documented with their physician. Patients sometimes may make advanced directives to participate in the research [16].

In most of the cases, the patient presents to the physicians in moderately advanced stages of MND-AD. There may not be any documentation of their advanced directives, including their resuscitation status. In these situations, appropriate substitute decision-makers for the patient need to be identified and documented to make decisions on behalf of the patient [4]. In those situations where there is no responsible substitute decision-maker from the family, an official of the government or court-appointed guardian needs to be appointed. The management of the patient's care should proceed in collaboration with the substitute decision-maker. Several clinical dilemmas occur in taking the treatment, care decisions, and end-of-life issues during the management of the patient as the disease progresses toward the terminal stages. Patients and their families' wishes must be respected throughout the course of MND-AD. Several of these issues related to capacity are discussed by Hope et al. [17].

In terms of the case presented here, the ethical questions mainly pertain to genetic testing as a method of establishing the cause of her major

neurocognitive disorder. Genetic testing, though available to rule out some known familial variants, may not be conclusive. Also, the lack of ready availability in the local hospitals and cost must be considered along with the family's wishes. Once the genetic variant is identified to be of a familial variety correlated with early-onset MND-AD, the family must understand the implications for themselves. Such testing must be performed only if pretest and posttest counseling and support are available for the family members. Finally, the definitive diagnosis of MND-AD in this case can only be made by brain biopsy, either antemortem or postmortem. The family's wishes either for personal or academic reasons must be sought in all such diagnostic dilemmas [24]. Invasive procedures such as a lumbar puncture for CSF analysis can be discussed with the family to improve diagnostic accuracy. CSF can be analyzed for proteins. Total tau (T-tau) in combination with neurofilament light (NFL) has potential for biomarkers for prediction of MND-AD [22].

Ethical issues will arise around the sexual behaviors noted in moderate and severe stages of dementia. In North American and Scandinavian countries, physician-assisted deaths are seriously considered in advanced stages of the disease. These are complicated with several controversies, and careful decisions must be taken within the legal realities of those countries.

Conclusion

As the world's population continues to age, the prevalence of major neurocognitive disorders will increase. Molecular genetics is furthering our understanding both in early diagnosis and research in new pharmacological interventions. Despite this, families and communities will likely experience more caregiver burden. Future planning and management of persons with Alzheimer's disease are fraught with several ethical and legal issues.

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