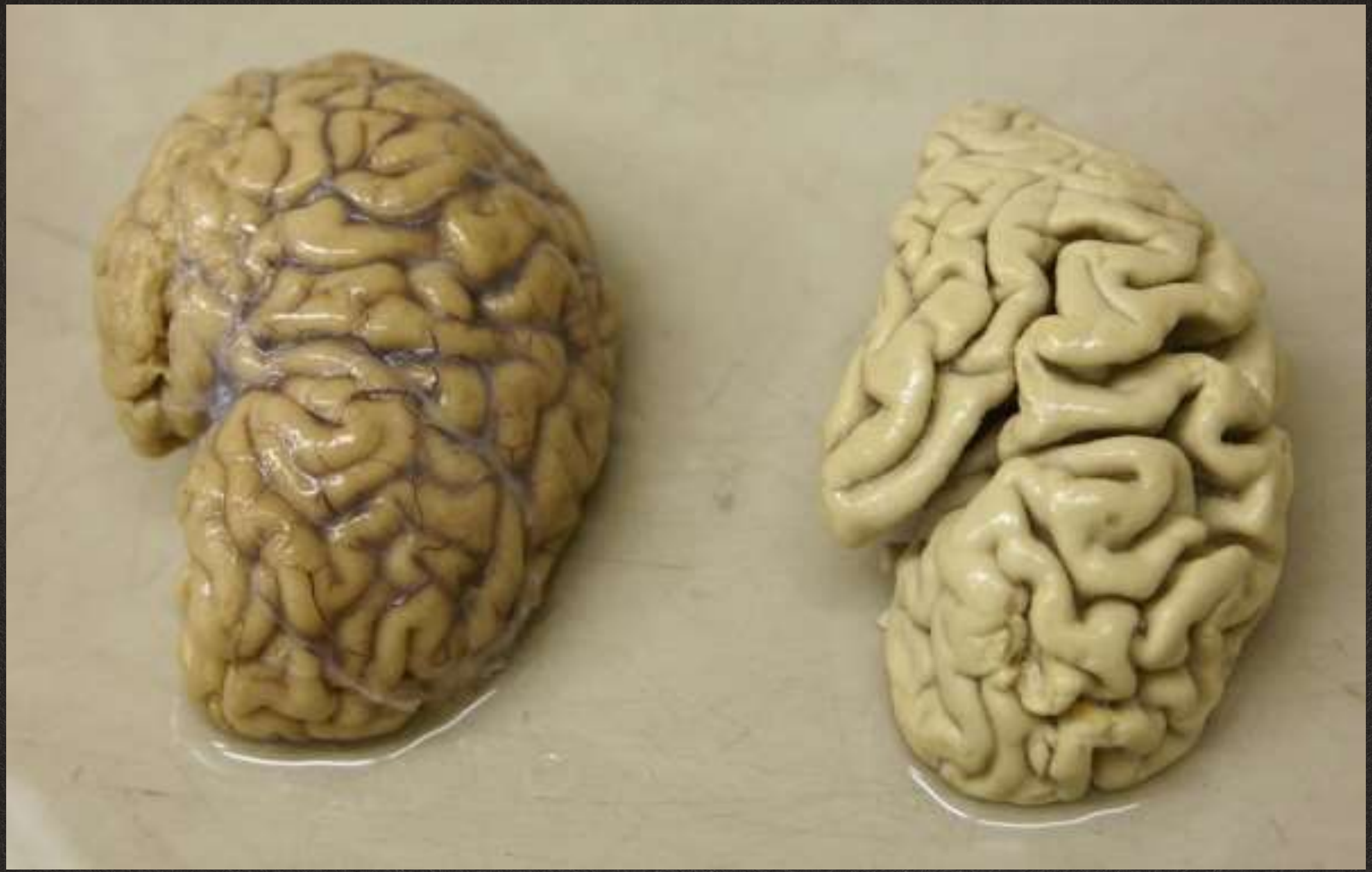
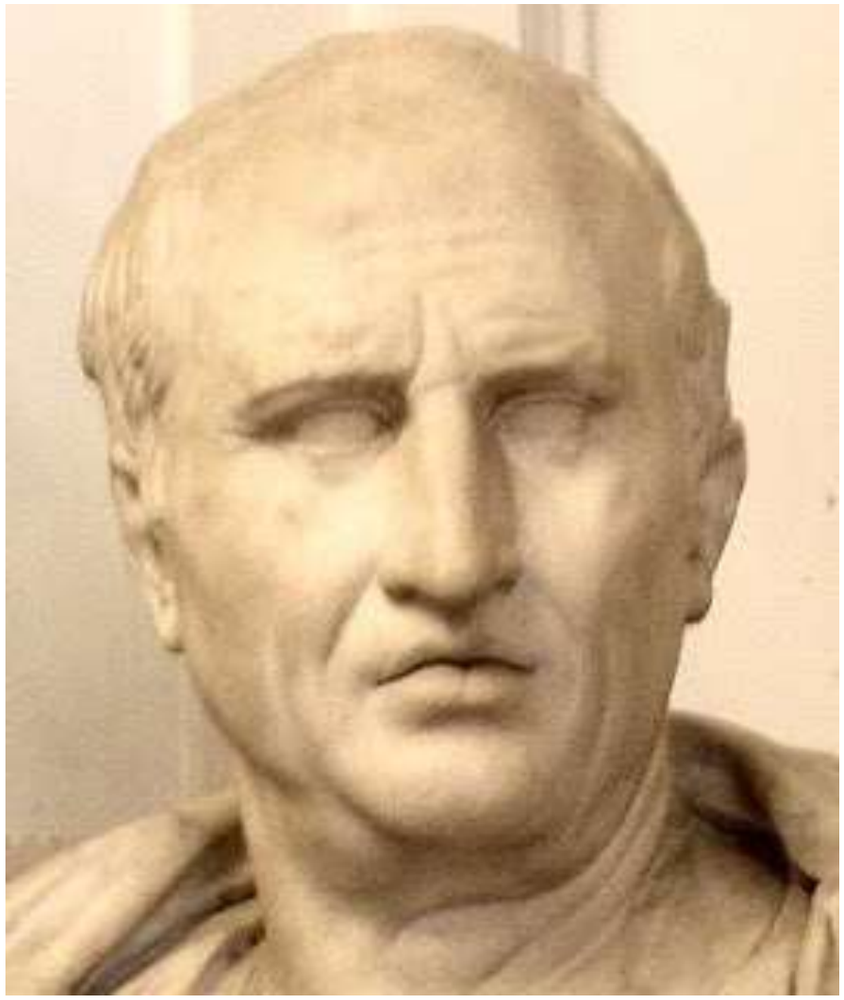




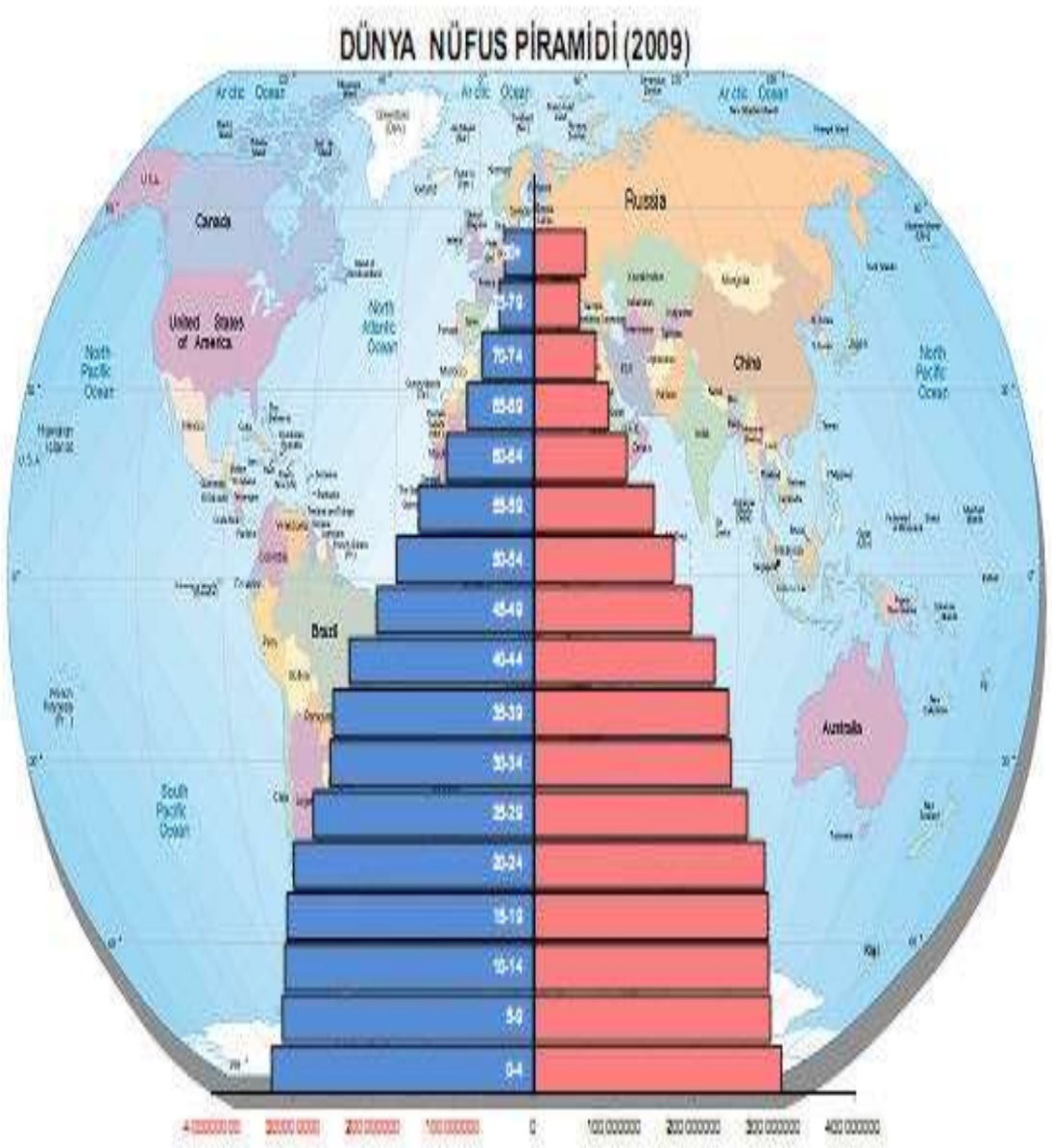
CİCERO'NUN CATO MAİOR'U İ.Ö.44'TE, ALTMIŞ İKİ YAŞINDAYKEN YAZDIĞI KABUL EDİLMEKTEDİR.

DE DİVİNATİON ADLI YAPITINDA CİCERO AHLÂKIN DÜŞÜK OLDUĞU BİR DÖNEMDE GENÇLİĞE DERS VERMEK, YARDIMDA BULUNMAK İSTEMİŞTİR.

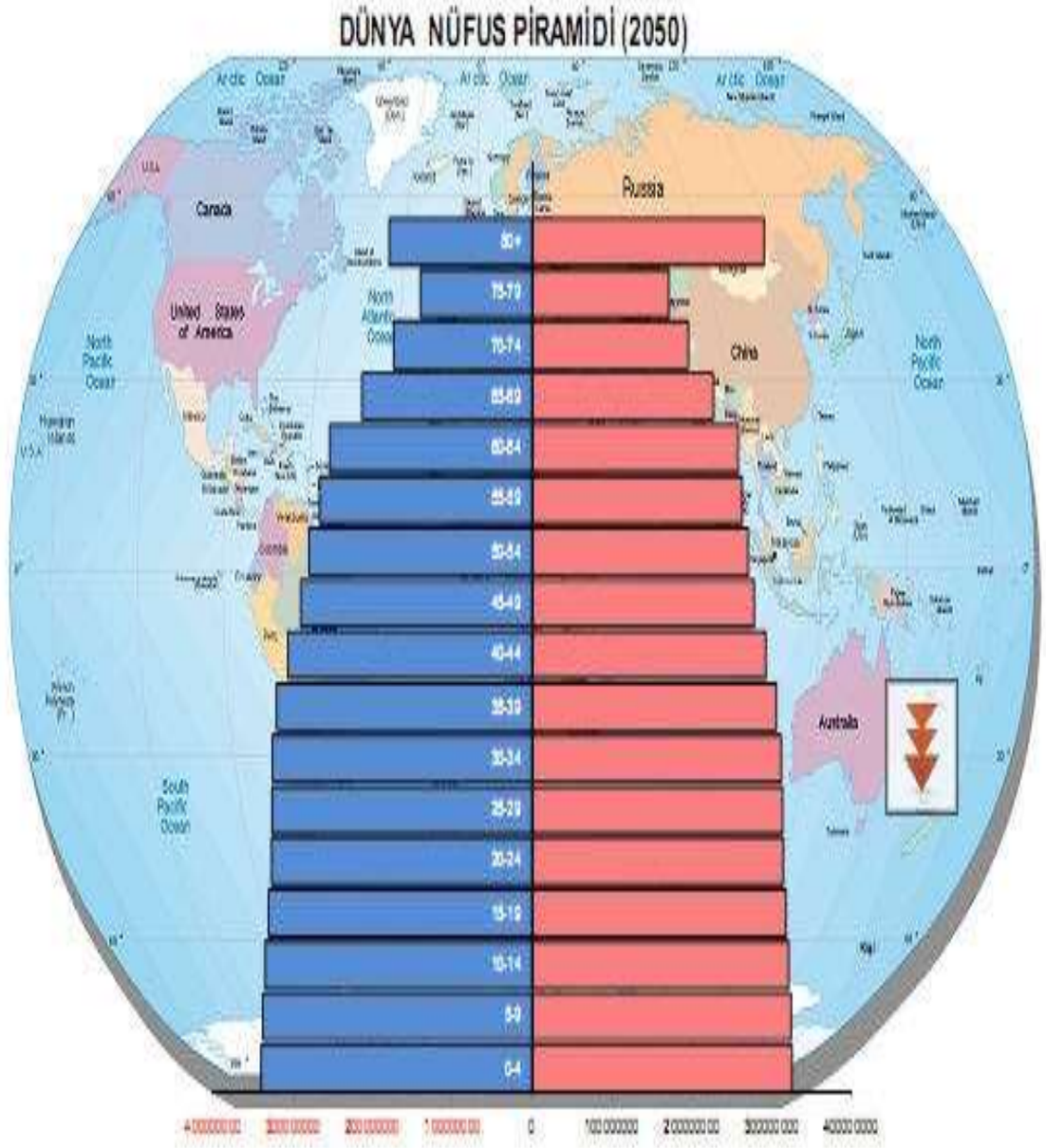
SCIPIO: C. LAELIUS ILE BEN ÇOĞU KEZ SENIN HER IŞTE GÖSTERDIĞIN ÜSTÜN VE YETKIN BILGELIĞIN KARŞISINDA HAYRANLIK DUYARIZ, AMA ASIL HAYRAN OLDUĞUMUZ ŞEY YAŞLILIĞIN SANA HIÇBIR ZAMAN YÜK OLMAYIŞI; OYSA YAŞLI KIMSELERIN ÇOĞUNA GÖRE YAŞLILIK ÖYLE KÖTÜ BIR ŞEYDIR KI "ONUN YÜKÜNÜ TAŞIMAK AETNA'YI TAŞIMAKTAN DAHA AĞIRDIR" DERLER.

KAYNAK:
HTTP://DUSUNDURENSOZLER.BLOGSPOT.COM.TR/2007

Dünya Nüfus Piramitleri : 2009-2050



www.cografyam.net



www.cografyam.net

2. DÜNYA SAVAŞI SONRASINDA AMERIKA VE AVRUPA'DA DOĞURGANLIK HIZININ ARTIŞIYLA 1950'LI YILLARDA «BEBEK PATLAMASI» (BABY BOOM) YAŞANDI. ÖNCEKILERDEN ÇOK DAHA KALABALIK OLAN BU KUŞAK, BÜYÜYÜP YETIŞKIN OLUNCA DAHA AZ SAYIDA ÇOCUK YAPTI. BU DA NÜFUSUN 2000'LERDEN ITIBAREN DAHA ÖNCE HIÇ GÖRÜLMEMIŞ ÖLÇÜDE YAŞLANMASINA YOL AÇTI.

«BEBEK PATLAMASI»NDAN «YAŞLI PATLAMASI»NA

onu ve Dünya Bankası verilerinden yaptığı derlemeye göre, 1960 yılında yaklaşık 3 m
1970 yılında 3,7 milyara,
1980 yılında 4,4 milyara,
1990 yılında 5,3 milyara,
2000 yılında 6,1 milyara,
2010 yılında 6,9 milyara,
2015 yılında 7.3 milyara ulaştı.

onu ve Dünya Bankası verilerinden yaptığı derlemeye göre, 1960 yılında yaklaşık 3 m
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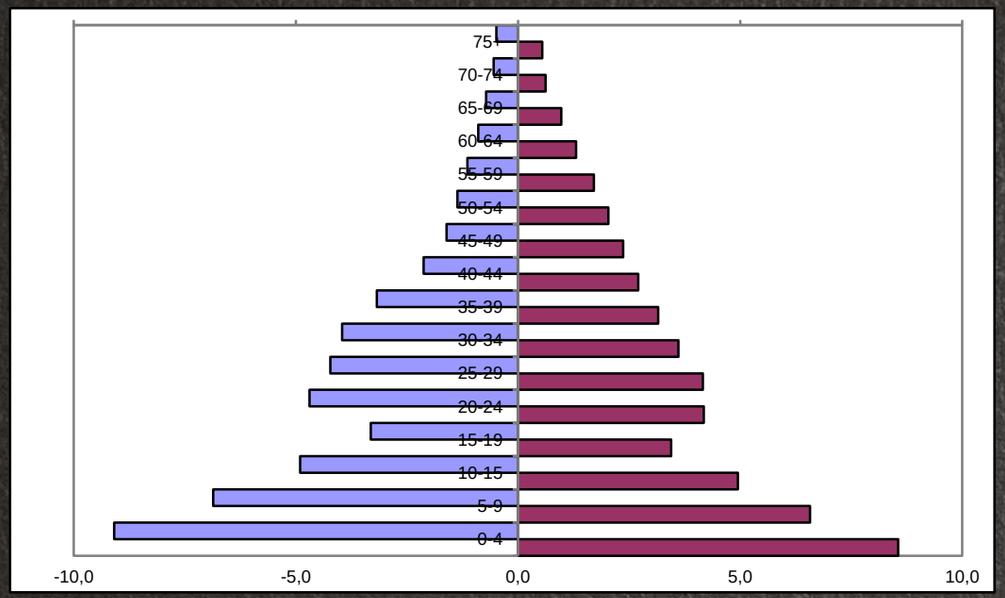
Fonu ve Dünya Bankası verilerinden yaptığı derlemeye göre, 1960 yılında yaklaşık 3
1970 yılında 3,7 milyara,
1980 yılında 4,4 milyara,
1990 yılında 5,3 milyara,
2000 yılında 6,1 milyara,
2010 yılında 6,9 milyara,
2015 yılında 7.3 milyara ulaştı.

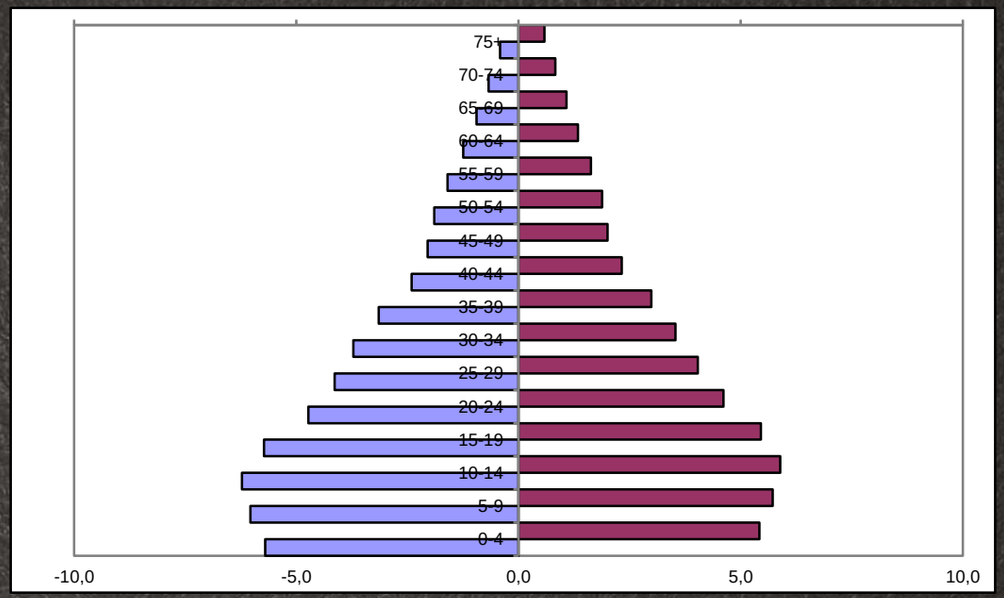
2050 yılında 9 milyara ulaşacak

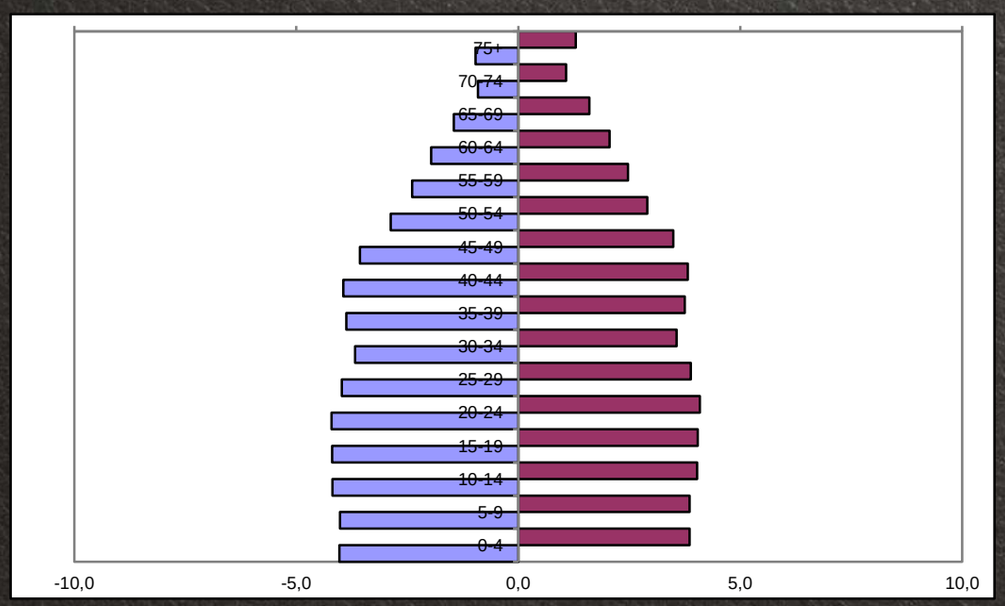
TÜRKİYE NÜFUS PİRAMİTLERİ : 1935-2000-2020-2050

1935

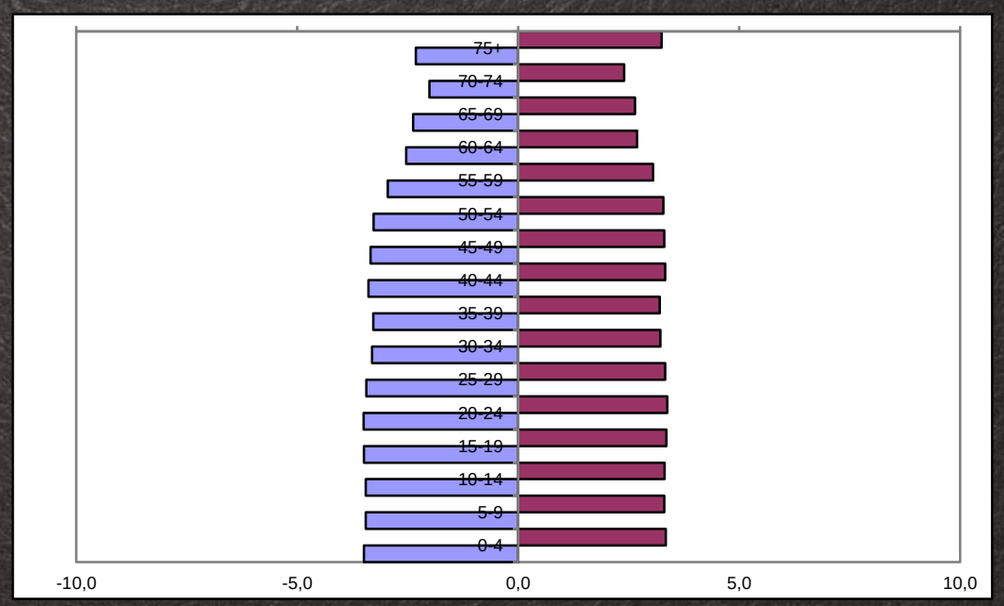


2000



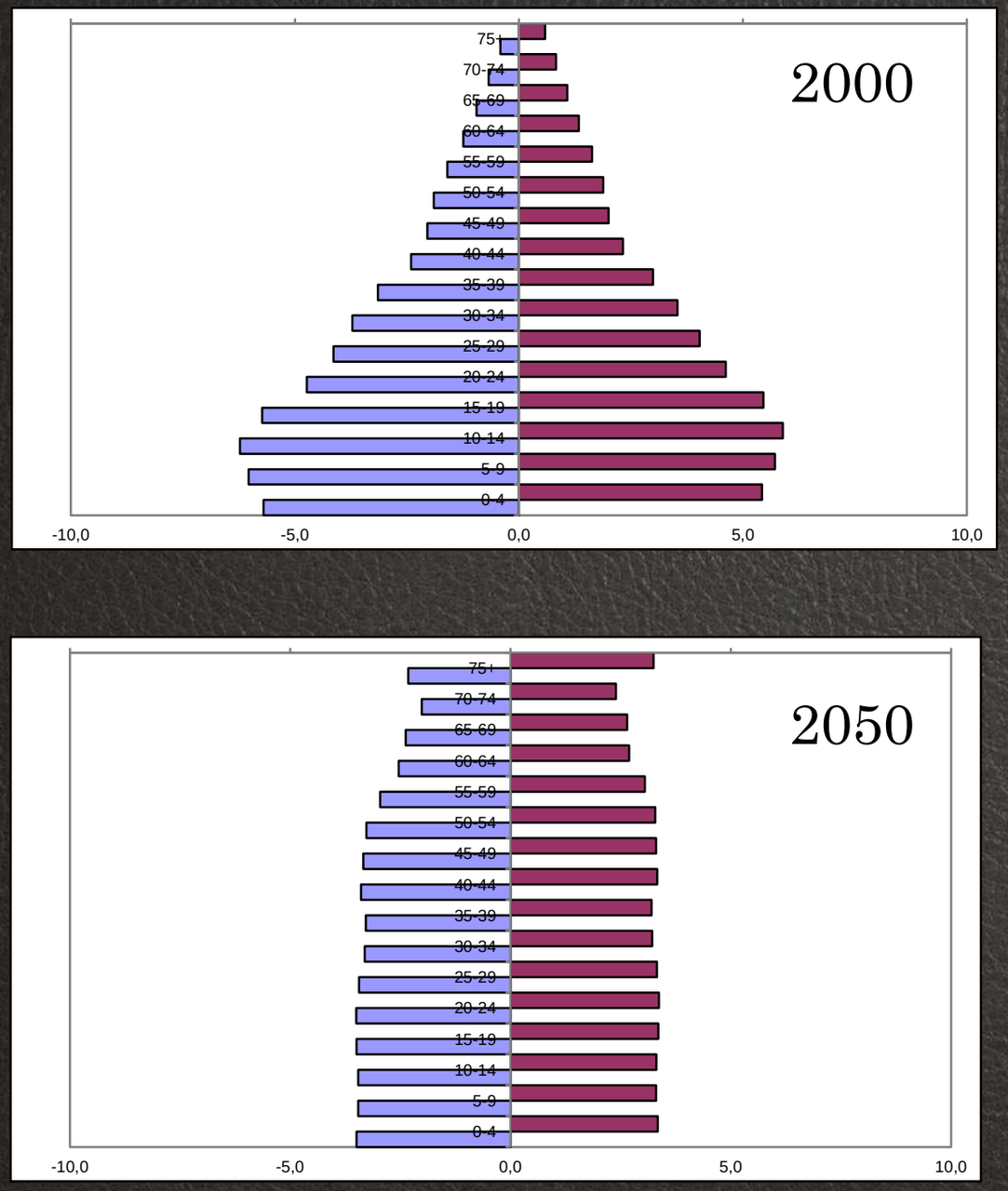


2020



2050

ÜLKEMİZİN NÜFUSU YAŞLANIYOR

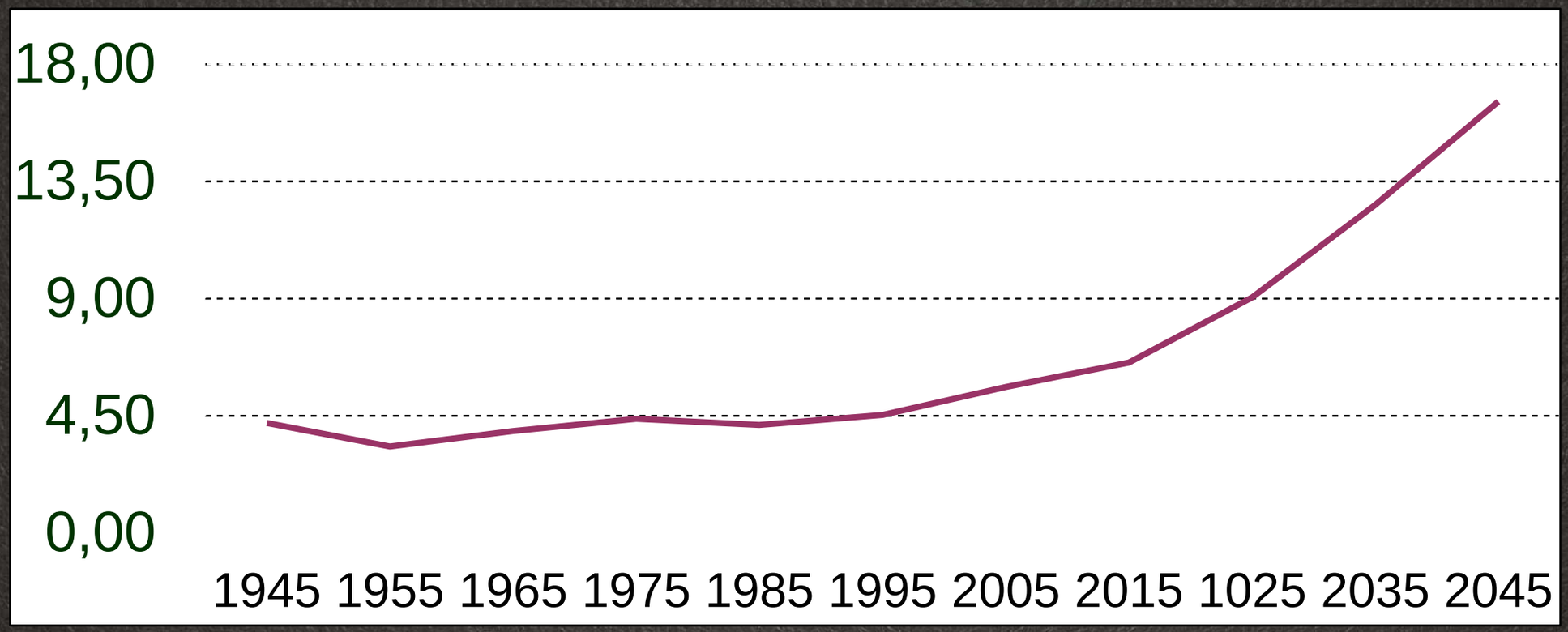


2025 yılında nüfusumuzun % 10'nun 65 yaş üzerinde,

2050 yılında nüfusumuzun %22' sinin 65 yaş üzerinde olacağı tahmin edilmektedir

65+ Yaş Nüfusun Toplam Nüfus içindeki Oranı Türkiye, 1945-2045

BİR ÜLKENİN YAŞLI NÜFUS OLARAK TANIMLANMASI İÇİN TOPLAM NÜFUSUNUN % 15'İNİN YAŞLI OLMASI GEREKİYOR.



Kaynak: UN Population Projections, 2005

TÜRKİYE, 2050 yılında,

4. ALZHEIMER ÜLKESİ OLACAK

ALZHEIMER HASTALIĞI

HASTA

HASTA BAKIM VEREN

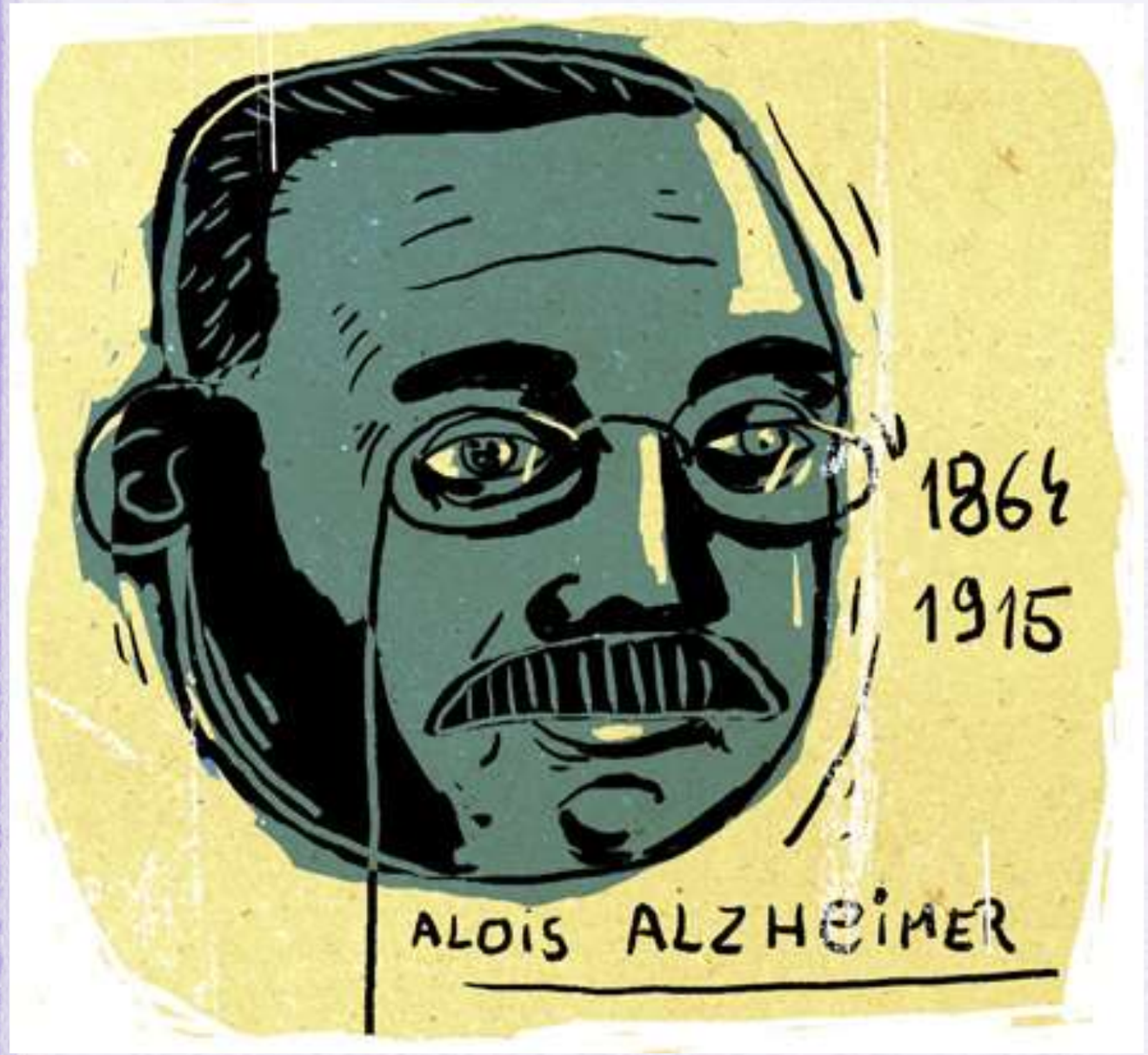
DOKTOR

SAĞLIK ÇALIŞANLARI

RESMİ KURUMLAR

SOSYAL GÜVENLİK KURUMU

YEREL YÖNETİMLER



HALK SAĞLIĞI PROBLEMİ

2015 de nüfusun, 600 milyon kişi yaşlı
2015 de Alzheimer Hasta sayısı 35.6 milyon

2050 de nüfusun, 2.2 milyar kişisi yaşlı
2050 de Alzheimer Hasta sayısı 115.4

2015 de nüfusun, 600 milyon kişi yaşlı
2015 de Alzheimer Hasta sayısı 35.6

Yaşlı sayısı 3.66 kat artacak
Alzheimer sayısı 3.5 kat artacak

2050 de nüfusun, 2.2 milyar kişisi yaşlı
2050 de Alzheimer Hasta sayısı 115.4

DÜNYADA 35.6 MİLYON KİŞİ ALZHEİMER HASTASI

2030 DA BEKLENEN RAKAM
65.7 MİLYON

2050 DE BEKLENEN RAKAM
115.4 MİLYON

Alzheimer's Disease International: World Alzheimer Report. http://www.alz.co.uk/research/world-report (2009). Accessed Feb 2012

Prevalence of dementia and associated risk factors in Middle Anatolia, Turkey.

J Clin Neurosci. 2009 Nov;16(11)

Arslantaş D[1], Ozbabalik D, Metintaş S, Ozkan S, Kalyoncu C, Ozdemir G, Arslantas A.

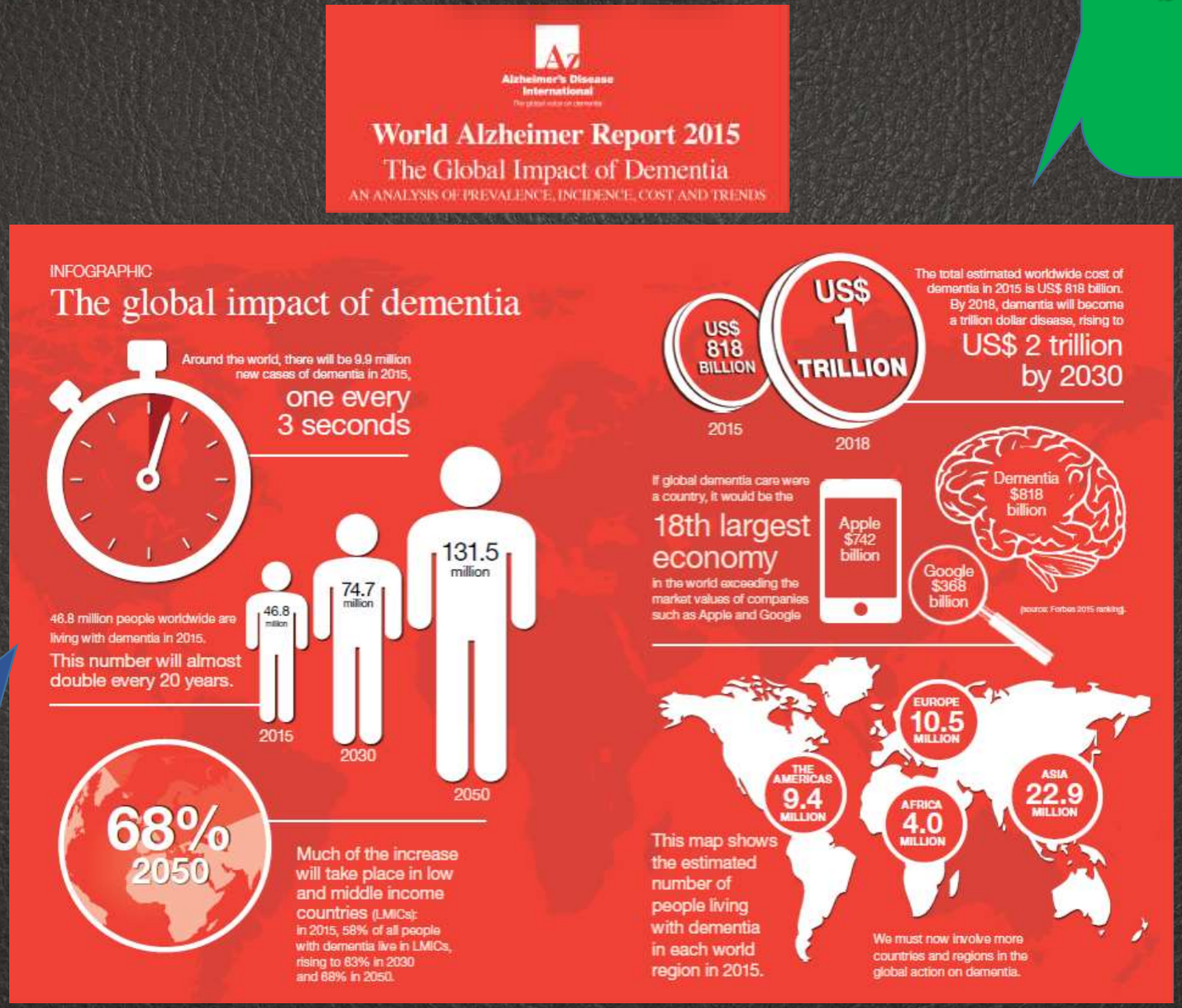
This study aimed to investigate the prevalence of various cognitive disorders in the older population (age 55 years and above) of Eskisehir, Turkey, by conducting a cluster sampled door-to-door survey. A total of 3100 inhabitants were screened with the Mini-Mental State Examination (MMSE) and a questionnaire concerning demographic, occupational and social data. Individuals (n=320) with MMSE scores of 25 were assessed according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and were investigated in the more detailed phase 2 study. The overall prevalence of dementia was 8.4%, although it ranged from 2.2% among those aged 55-59 years to 5.3% among those aged 60-64 years, and to 30.4% among those aged 75 or above. Vascular dementia was the most common type (51.1%), followed by Alzheimer's dementia (48.8%). In a very small proportion of individuals (0.1%), dementia was due to other causes such as B12 deficiency, a tumour or hydrocephalus. Significant risk factors for dementia were female sex, low education, age, living in a rural area and a family history of dementia.

ESKİŞEHİR İL VE İLÇELERİNDE, DEMANS SIKLIĞI 60 YAŞ ÜSTÜ % 8.4 OLUP BUNUN % 48.8 ALZHEİMER HASTALIĞI OLARAK TANINDI.

Alzheimer Hastalığı Güncel Durum 2015 Dünya Alzheimer Raporu Diyor Ki:

Global Demans tedavisi bir ülke olsaydı, dünyadaki en büyük 18. ekonomiyi oluşturuyor olacaktı.

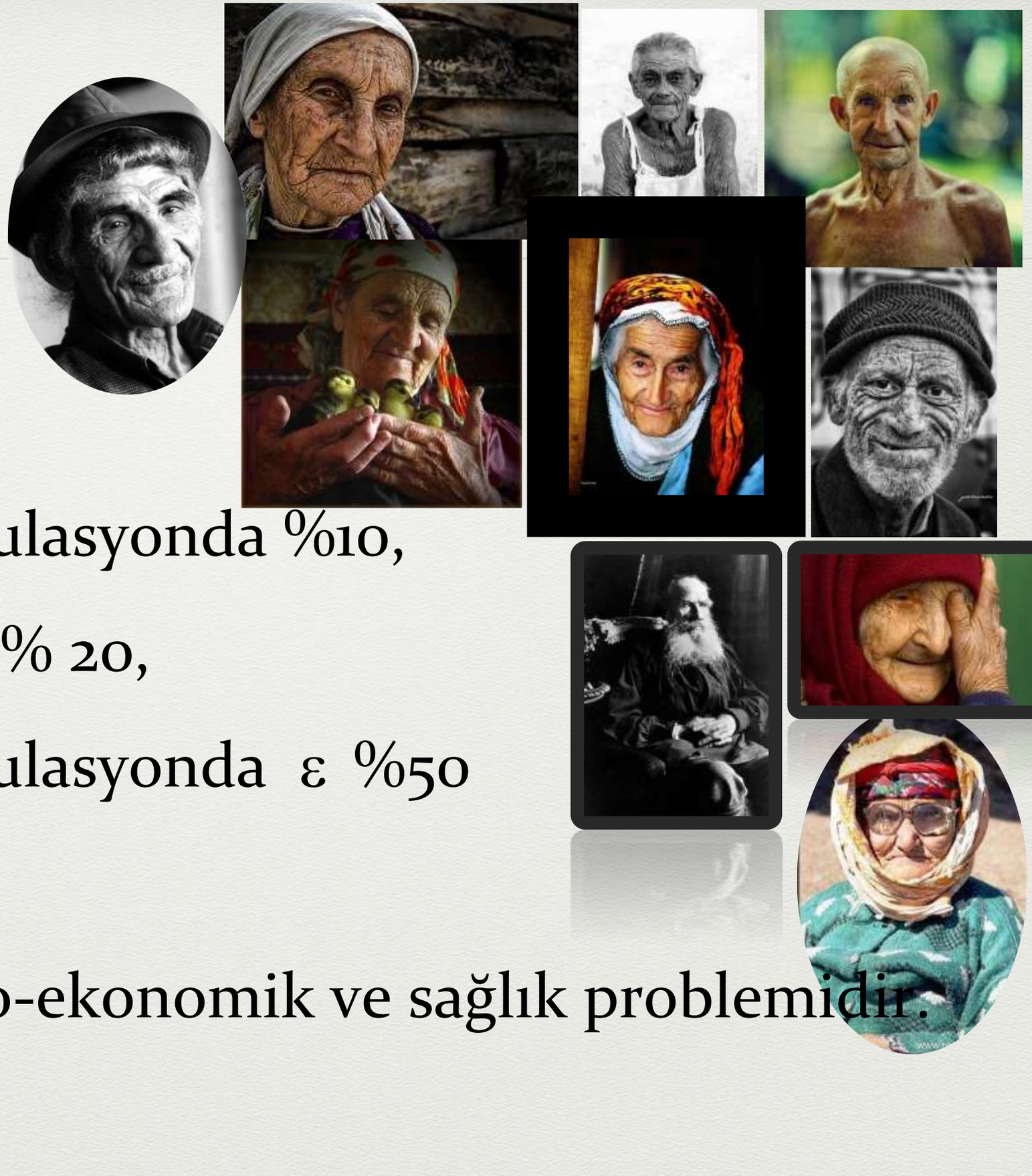
‘Her 3 saniyede 1 yeni Alzheimer Hastalığı tanısı konuluyor. ‘
‘2015 yılı itibarı ile dünyada yaklaşık 47 milyon Alzheimer Hastası vardı.’
‘Her 20 yılda bir yaklaşık 2 katına çıkacak.’



- Demans, küresel düzeyde yaklaşık 600 milyar ABD dolarına mal oluyor.

- Demans hastalarının bakımına harcanan paranın, dünya genelinde gayrı safi milli hasılanın yüzde 1'inden daha fazlasına mal olduğu hesaplanmaktadır.

- İktisatçılara göre, “Eğer demans ve benzeri hastalıkların bakımı bir ülke olsaydı, dünyanın ekonomisi en büyük ülkeler sıralamasında, Türkiye ile Endonezya arasında bir yerlerde, yani 18'inci sırada gelebilirdi.



Demans

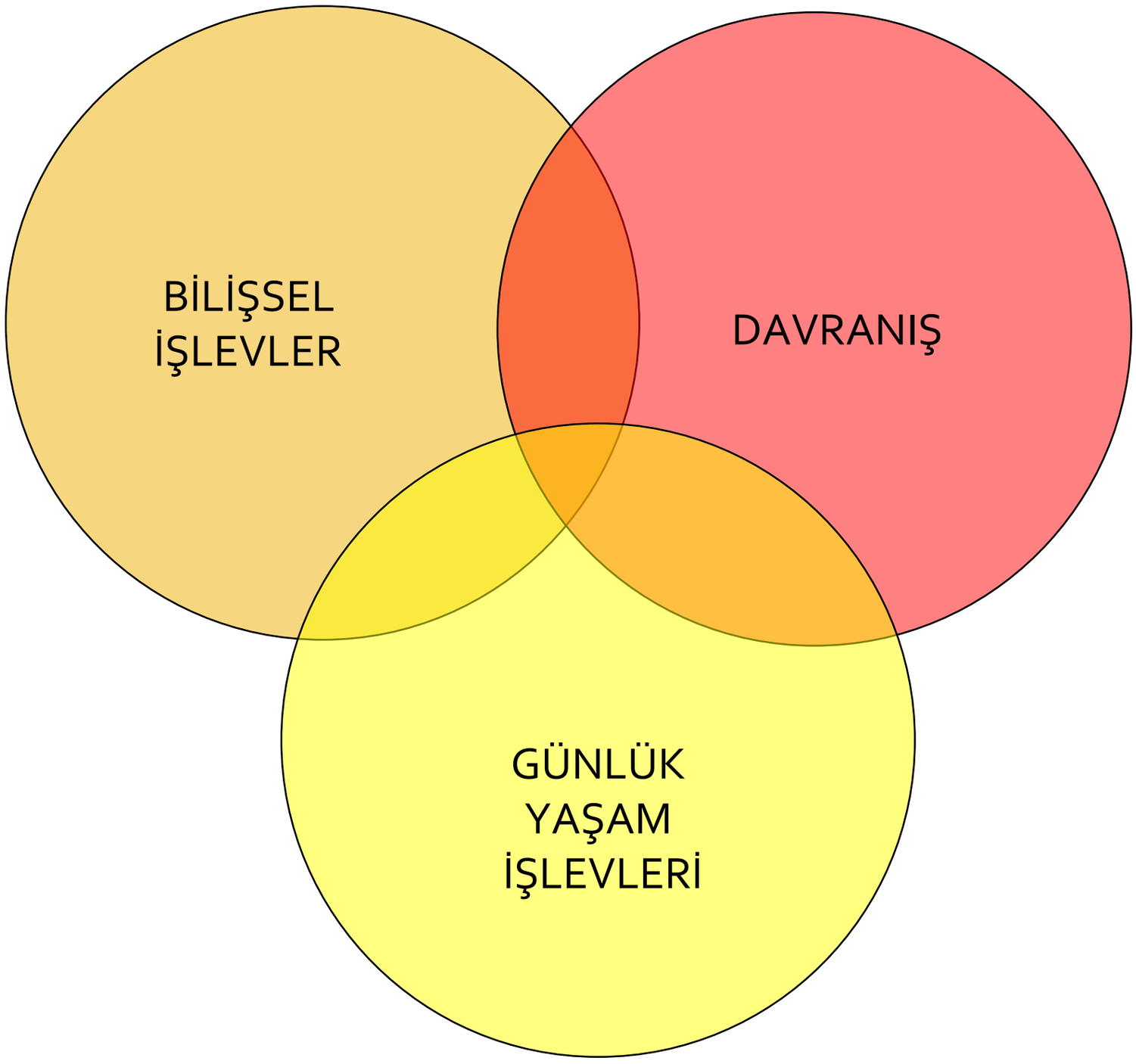
65 yaş üzeri populasyonda %10,

75 - 84 yaşlarda % 20,

85 yaş üzeri populasyonda ε %50

Önemli bir sosyo-ekonomik ve sağlık problemidir.

ALZHEIMER HASTALIĞI'nda ETKİLENEN ALANLAR

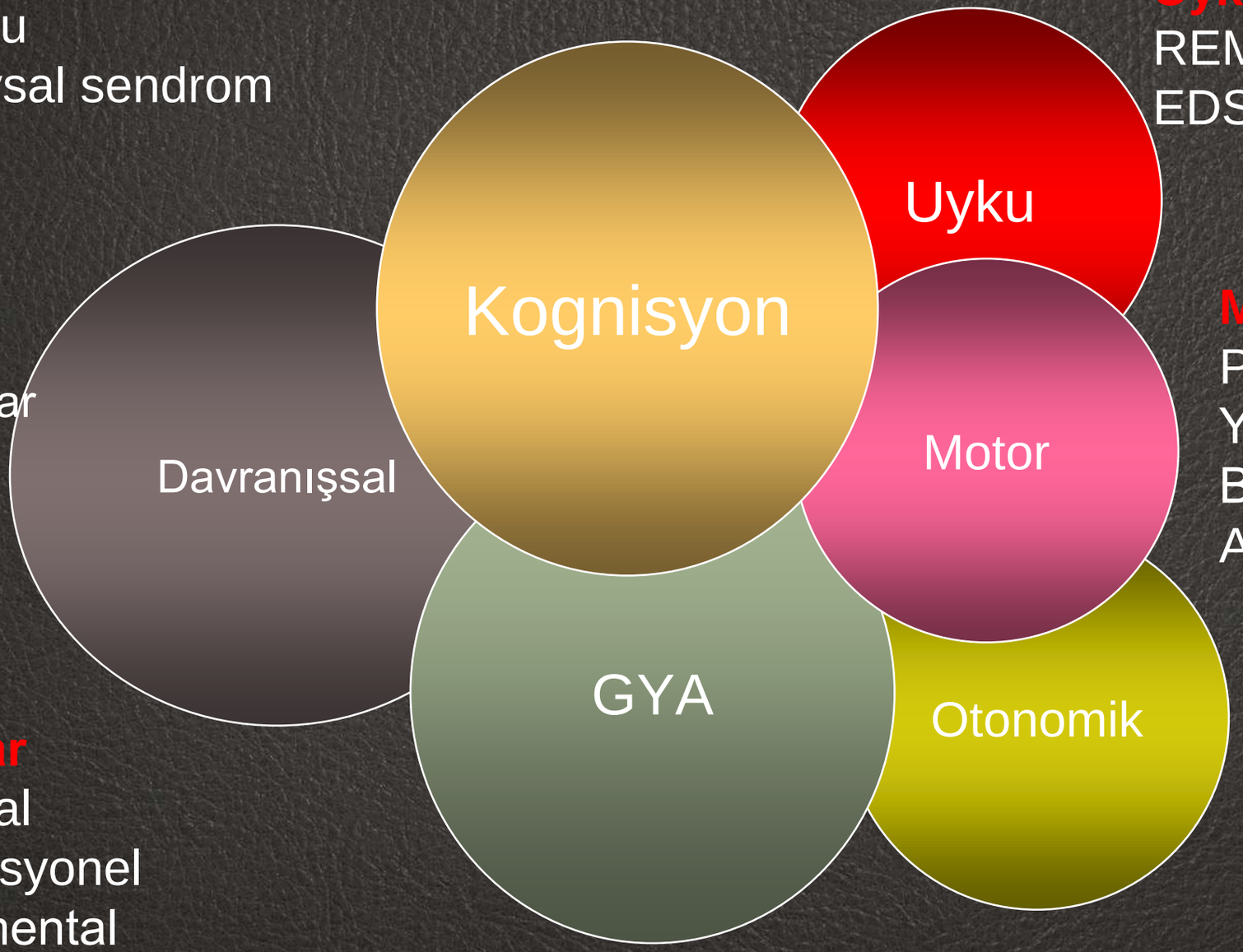


DEMANS SENDROMUNDA KARDİNAL VE EŞLİKÇİ BULGULAR

Kognitif
Bellek sendromu
Diseksekutif sendrom
Dil sendromu
Görsel-uzaysal sendrom

Uyku
REM-UBD
EDS

Davranışsal
Apati
Disinhibisyon
Halüsinasyonlar
Delüzyonlar
Depresyon
Anksiete
Ajitasyon



Motor
Parkinsonizm
Yürüyüş bozukluğu
Bakış paralizisi
Amyotrofi

GYA'lar
Finansal
Navigasyonel
İnstrumental
Domestik
Hijyen

Otonomik
İnkontinans
Ortostatism
Impotans
Konstipasyon

1906-1960: ILK KEŞIF

1970-1979: MODERN ÇALIŞMALAR

1980-1989: FARKINDALIK

1990-1999: ACIL TEDAVILER

2000-2009: ILERLEME VE UMUT

2010-2019: ULUSAL VE ULUSLARARASI AJANDALAR

Department of medical history

Auguste D and Alzheimer's disease

Konrad Maurer, Stephan Volk, Hector Gerbaldo

On Nov 4, 1906, Alois Alzheimer gave a remarkable lecture,[1] in which he described for the first time a form of dementia that subsequently, at the suggestion of Emil Kraepelin,[2] became known as Alzheimer's disease. In his lecture, at the 37th Conference of South-West German Psychiatrists in Tübingen, Alzheimer described a patient called Auguste D, a 51-year-old woman from Frankfurt who had shown progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence. At necropsy, there were plaques, neurofibrillary tangles, and arteriosclerotic changes. The eponym Alzheimer, originally used to refer to presenile dementia, came into later use for the largest cause of primary dementia—senile dementia of the Alzheimer type (SDAT). Here, we describe the discovery and contents of the file of Auguste D, which had not been seen since 1909.

Figure 1: **Cover of the file of Auguste D**
Admitted Nov 25, 1901, died April 8, 1906. 36 × 23·5 cm.

Alzheimer and Auguste D

Alzheimer was born on June 14, 1864, in Marktbreit, Germany, a small village near Würzburg. He studied medicine at the universities of Berlin, Tübingen, and Würzberg, where he wrote his doctoral thesis *Über die Ohrenschmalzdrüsen* (on ceruminal glands) in 1887, producing his first histological plates. In December, 1888, he began his medical career as a resident at the Hospital for the Mentally Ill and Epileptics, Frankfurt am Main, and subsequently was promoted to senior physician.

Alzheimer's research interests were wide ranging and included not only dementia of degenerative and vascular (arteriosclerotic) origin but also psychoses, forensic psychiatry, epilepsy, and birth control. His interest in the neuropathology of dementing disorders was shared by his colleague Franz Nissl, who came to Frankfurt in March, 1889. It was Nissl who provided Alzheimer with new histopathological techniques for studying nervous disorders.

On Nov 25, 1901, Auguste D was admitted to the Frankfurt hospital, where she was examined by Alzheimer. She had a striking cluster of symptoms that included reduced comprehension and memory, as well as aphasia, disorientation, unpredictable behaviour, paranoia, auditory hallucinations, and pronounced psychosocial impairment.

In 1903, Alzheimer left Frankfurt, and, after a short stay in Heidelberg, moved to the Royal Psychiatric Clinic, Munich, whose director was Kraepelin. There, Alzheimer continued to follow Auguste D's case until her death in Frankfurt on April 8, 1906, after which he went on to study the neuropathological features of her illness.

Auguste D and her file

On Dec 19, 1995, the 80th anniversary of Alzheimer's death was commemorated at his birthplace in Marktbreit with the inauguration of his house as a museum and conference centre. Eli Lilly purchased the house, which has been renovated under the direction of Ulrike Maurer. Previously, we had conducted an intensive search for the file of Auguste D, which had been lost since its description by Perusini[3] in 1909. We had been looking for it for many years; only 2 days after the 80th anniversary we found it in the archives of our own department in Frankfurt.[4]

After 90 years, the blue-coloured cardboard file was still in good condition (figure 1): it contained a total of 32 sheets with the patient's admission report, an attestation, and three versions of the case history—one in Latin script and two in the now outdated German "Sütterlin" script. The first Latin script, already published by Perusini[3] and subsequently translated,[5] begins with questions about her husband, followed by clinical findings, the details of the course of her disease, and a report on her death, including a histopathological diagnosis. The part written in Latin is followed by a nearly identical copy in Sütterlin. A small sheet of paper with the handwriting of Auguste D dated by Alzheimer shows "amnestic writing disorder" so named by Alzheimer himself (figure 2). Alzheimer's handwritten notes, also in Sütterlin, document in detail his patient's symptoms during the first 4 days of her stay in hospital. In between Alzheimer's notes are additional samples of Auguste D's attempts to write her name. The file also contains four photographs of her (the most impressive is shown in figure 3) and a report about the course of the disease, which consisted of concise notes starting on June 29, 1905, and ending on the day of her death on April 8, 1906. Several attestations and an application form for hospitalisation of a mentally ill person together with a one-page case report from the Royal Psychiatric Department, Munich, conclude the file.

Figure 2: **Auguste D's handwriting**
Dated by Alzheimer (26. XI. Frau Auguste D Frankfurt / Main).

Alzheimer's notes in the file begin on Nov 26, 1901. He asked simple questions and wrote down Auguste D's answers systematically. He resumed questioning on Nov 28, 29, and 30 on four handwritten pages.

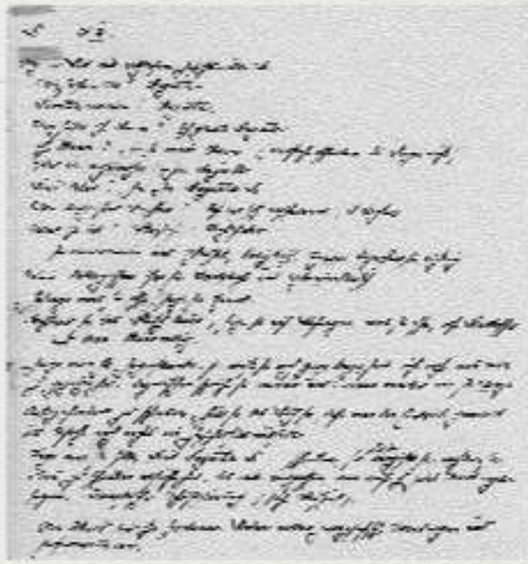
The file begins as follows (our italics denote Auguste D's answers, and each translated passage is followed by figures of the original pages in the file):

Nov 26, 1901

She sits on the bed with a helpless expression. What is your name? *Auguste.* Last name? *Auguste.* What is your husband's name? *Auguste, I think.* Your husband? *Ah, my husband.* She looks as if she didn't understand the question. Are you married? *To Auguste.* Mrs D? *Yes, yes, Auguste D.* How long have you been here? She seems to be trying to remember. *Three weeks.* What is this? I show her a pencil. *A pen.* A purse and key, diary, cigar are identified correctly. At lunch she eats cauliflower and pork. Asked what she is eating she answers *spinach.* When she was

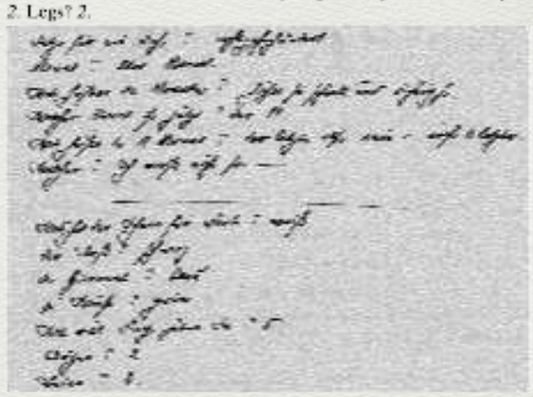
Figure 3: **Auguste D**
Photograph dated November, 1902.

chewing meat and asked what she was doing, she answered *potatoes* and then *horseradish.* When objects are shown to her, she does not remember after a short time which objects have been shown. In between she always speaks about twins. When she is asked to write, she holds the book in such a way that one has the impression that she has a loss in the right visual field. Asked to write Auguste D, she tries to write Mrs and forgets the rest. It is necessary to repeat every word. Amnestic writing disorder. In the evening her spontaneous speech is full of paraphrasic derailments and perseverations.



Extracts from Nov 29, 1901

. . . What year is it? *Eighteen hundred.* Are you ill? *Second month.* What are the names of the patients? She answers quickly and correctly. What month is it now? *The 11th.* What is the name of the 11th month? *The last one, if not the last one.* Which one? *I don't know.* What colour is snow? *White.* Soot? *Black.* The sky? *Blue.* Meadows? *Green.* How many fingers do you have? *5.* Eyes? *2.* Legs? *2.*

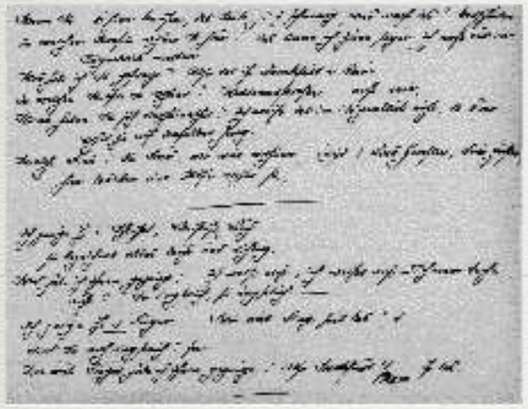


. . . If you buy 6 eggs, at 7 dimes each, how much is it? *Differently.* On what street do you live? *I can tell you, I must wait a bit.* What did I ask you? *Well, this is Frankfurt am Main.* On what street do you live? *Waldemarstreet, not, no. . . .* When did you marry? *I don't know at present. The woman lives on the same floor.* Which woman? *The woman where we are living.* The patient calls *Mrs G, Mrs G, here a step deeper, she lives. . . .* I show her a key, a pencil and a book and she names them correctly. What did I show you? *I don't know, I don't know.* It's difficult isn't it? *So anxious, so anxious.* I show her 3 fingers; how many fingers? *3.* Are you still anxious *Yes.* How many fingers did I show you? *Well this is Frankfurt am Main.*

Lancet 1997; **349**: 1546–49

Department of Psychiatry and Psychotherapy I (Prof K Maurer MD, H Gerbaldo MD) **and II** (S Volk MD); **Johann Wolfgang Goethe University, Heinrich-Hoffmann Straße 10, 60528 Frankfurt am Main, Germany.**

Correspondence to: Prof Konrad Maurer



The patient is asked to recognise objects by touch, with her eyes closed. A toothbrush, sponge, bread, breadroll, spoon, brush, glass, knife, fork, plate, purse, Mark, cigar, key. She recognises them quickly and correctly. By touch she calls a brass cup *a milk jug*, *a tea-spoon*, but when she opens her eyes she immediately says *a cup*.

Writing, she does it as already described. When she has to write Mrs Auguste D, she writes Mrs and we must repeat the other words because she forgets them. The patient is not able to progress in writing and repeats, *I have lost myself*.

Reading, she passes from one line to the next and repeats the same line three times. But, she correctly reads the letters. She seems not to understand what she reads. She stresses the words in an unusual way. Suddenly she says *twins, I know Mr Twin*. She repeats the word twin during the whole interview.

The reactions of the pupils to light and accommodation are instantaneous. Tongue has normal mobility, dry, yellow-red-brown. No disturbance in speech articulation. She frequently interrupts herself in the articulation of words during the interview (as if she did not know whether she had said something correctly or not). She has dentures. No facial nerve differences. Muscular strength at the left side considerably reduced compared with the right side. Patellar reflex normal. Radial reflex is slightly (but not relevantly) rigid. Cardiac ictus is not felt. Cardiac obtusity not enlarged. The second pulmonary and aortic tones are not accentuated.

During physical examination she cooperates and is not anxious. She suddenly says *Just now a child called, is he there?* She hears him calling..., she knows Mrs Twin. When she was brought from the isolation room to the bed she became agitated, screamed, was non-cooperative; showed great fear and repeated *I will not be cut. I do not cut myself.*

Alzheimer's report in Sütterlin ends on Nov 30, 1901. The two other versions, in Sütterlin and Latin, continue to document the course of Auguste's disease. In the Latin version, an entry from Nov 7, 1905, states: "Tendency to develop a decubitus since the beginning of 1906. Ulcerations at the sacral and left trochanteric area with a size of about 5 cm. Very weak, high fever up to 40°C within the last days. Pneumonia in both inferior lobes".

The day of Auguste's death on April 8, 1906, was not mentioned by Alzheimer but by his other two (unnamed) colleagues, who wrote the following report (in Latin) about the decay and the neuropathological diagnosis:

April 8, 1906
During the morning *exitus letalis*; cause of death: septicaemia due to decubitus; anatomical diagnosis: moderate hydrocephalus (external internal); cerebral atrophy; arteriosclerosis of the small cerebral vessels; ? ; pneumonia of both inferior lobes; nephritis.

The eponym Alzheimer

After Auguste D's death, Alzheimer asked for her records and brain to be sent to Munich, to where he had moved in 1903. Within 6 months he presented his findings to the Tübingen meeting, the abstracts of which were published in the same year.[1] Alzheimer's was the 11th contribution. However, only the title of his presentation was announced with a statement in parentheses that the lecture "was not appropriate for a short publication".

11. Herr Alzheimer (München): Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde (zu kurzem Referat nicht geeignet).

It was not until the following year, in 1907, that Alzheimer published his lecture[1] under the title "A characteristic serious disease of the cerebral cortex". He described "the case of a patient who was kept under close observation during institutionalisation at the Frankfurt Hospital and whose central nervous system had been given to me by director Sioli for further examination". Alzheimer described, without identifying her, a "51-year-old woman" who showed "as one of her first disease symptoms a strong feeling of jealously towards her husband. Very soon she showed rapidly increasing memory impairments; she was disoriented carrying objects to and fro in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly... After 4½ years of sickness she died".

Alzheimer also described the histopathological findings of this disease. He reported peculiar changes in the neurofibrils: "In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability". He went on to describe the typical plaques, later named after him: "Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex". Alzheimer continues: "all in all we have to face a peculiar disease process. Such peculiar disease processes have been verified recently in considerable numbers".

We learn more about this patient in an article by Perusini, "On histological and clinical findings of some psychiatric diseases of older people", published in 1909.[3] On Alzheimer's suggestion, Perusini "examined four cases characterised by clinical and especially histopathological signs". In this article, Auguste D was reinvestigated with respect to her symptoms and histopathology as case No 1. For the first time the initials of her surname, complete given name, and profession of her husband were mentioned ("D Auguste, wife of an office clerk, aged 51½ years"). Perusini thanked Sioli from Frankfurt am Main for the use of the case history and the brain for microscopic research. Thus, Perusini's case No 1 is identical with the case described by Alzheimer in his 1907 paper,[1] a fact that was not completely clear until now.

Perusini referred to the Latin version of Auguste D's case history; he presented detailed histopathological findings together with six illustrations showing amyloid plaques and neurofibrillary tangles. In summary, he stated:[3] "The pathological process recalls main features of senile dementia; however, the alterations in the cases described are more far reaching, although some of them represent presenile diseases".

Besides the two important publications of Alzheimer in 1907 and Perusini in 1909 on Auguste D, Kraepelin must have known of other reports: Bonfiglio[7] reported in 1908 on a similar patient, aged 60, who had similar symptoms and histopathology; in 1907, Fischer[8] had published a detailed description of histopathological changes in dementia; and then there was Alzheimer's 1911 report[9] (which appeared 1 year after the eponym had been introduced by Kraepelin) in which he described his second case of dementia (Johann F). In the discussion were drawings of typical changes in the neurofibrils (figure 5), which were from his first case (Auguste D).

In the 8th edition (1910) of *Handbook of Psychiatry*, Kraepelin[2] stated that "a particular group of cases with extremely serious cell alterations was described by Alzheimer". The necropsy findings showed changes that "represent the most serious forms of senile dementia. The plaques were excessively numerous and almost one-third of the cortical cells had died off. In their places were peculiar, deeply stained bundles of neurofibrils". He mentioned "Alzheimer's disease" for the first time, stating, "The clinical interpretation of this Alzheimer's Disease is still unclear. Although the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia, the fact is that this disease sometimes starts as early as in the late forties". In the chapter on senile dementia, there is an illustration of "fibrillary patterns in Alzheimer's disease" from the third layer of the frontal cortex. The neurofibrillary tangles in this figure resemble those drawn in 1911 by Alzheimer.[9]

Figure 5: **Neurofibrillary tangles from Auguste D, drawn by Alzheimer**
From ref 9.

Kraepelin introduced the eponym Alzheimer's disease, but why did he use Alzheimer's name, and not Perusini's, Bonfiglio's, or Fischer's? Since Alzheimer described the two cases, and since Perusini republished the Auguste D case (with photographs and drawings of the histopathological findings), we are convinced that the eponym was based on Alzheimer's 1907 report of Auguste D's case. Moreover, she only showed neuritic plaques and neurofibrillary tangles typical of the disease.

Several hypotheses to account for the haste with which Kraepelin created the new eponym have been put forward.[9,11] Beach[11] says that Kraepelin did so for scientific reasons, because he believed that Alzheimer had discovered a new disease. Another reason might have been the existing rivalry between his department and that of Pick in Prague (where Fischer also worked) and the desire for prestige for his Munich laboratory. Also plausible is Kraepelin's wish to show the superiority of his school over psychoanalytical theories and to show (vis-a-vis Freud) that some mental disorders were organically based. The most likely explanation, however, is the close collaboration between Kraepelin and Alzheimer, and Kraepelin's awareness of Alzheimer's clinical and scientific work on presenile cases.

Auguste D's dementia

There are doubts about the diagnosis of Auguste D's illness, and other diagnoses have been put forward, especially arteriosclerosis of the brain.

Both descriptions of Auguste D's dementia by Alzheimer and Perusini confirm that Auguste D had a degenerative and not a vascular form of dementia. Alzheimer mentioned the miliary foci (later called senile plaques), which represented the sites of deposition of a peculiar substance in the cerebral cortex. This substance has since turned out to be β-amyloid protein. Alzheimer showed clumps and condensations of intracellular fibrils and called them "neurofibrillary degeneration".

At Alzheimer's suggestion, Perusini restudied the brain of Auguste D and found "that the large cerebral vessels, the arterial circle of Willis and the Sylvian arteries showed no significant signs of arteriosclerosis"; only "some regressive alterations of the arterial wall" were noted. Perusini confirmed the presence in Auguste D of neuritic plaques and neurofibrillary tangles.

In summary, the clinical and histopathological findings of Auguste D accord with the ICD-10, DSM-III-R, and CERAD[12] definitions of Alzheimer's disease. There can be little further doubt in view of Alzheimer's observations published in 1911, in which he refers to the presence of neurofibrillary tangles in the second and third layers of the cortex in a brain slice of his first case (ie, Auguste D) (figure 5).

Alzheimer anticipated the debate about which type of dementia Auguste D may have had by his remark in 1907:[1] "a histopathological analysis at a later point will show the peculiarity of this case". Our next goal is to find the brain sections of Auguste D so that we can corroborate Alzheimer's original findings.

We thank Heiko Braak for critical reading of the histopathological part of the manuscript and for his suggestions; and Doris Plocher for her help in deciphering Alzheimer's handwriting.

References

1 Alzheimer A. Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde. *Neurologisches CentralBlatt* 1906; 23: 1129–36.
2 Kraepelin E. Psychiatrie: Ein Lehrbuch für Studierende und Ärzte. Leipzig: Barth, 1910: 593–632.
3 Perusini G. Über klinisch und histologisch eigenartige psychische Erkrankungen des späteren Lebensalters. In: Nissl F, Alzheimer A, eds. Histologische und Histopathologische Arbeiten. Jena: Verlag G Fischer, 1909: 297–351.
4 O'Brien C. Auguste D and Alzheimer's disease. *Science* 1996; 273: 28.
5 Bick K, Amaducci L, Pepeu G, eds. The early story of Alzheimer's disease. Padova: Liviana Press, 1987: 82-85.
6 Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin* 1907; 64: 146–48.
7 Bonfiglio F. Di speciali reperti in un caso di probabile sifilide cerebrale. *Riv Sper Freniatria* 1908; 34: 196–206.
8 Fischer O. Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmäßige Veränderung der Hirnrinde bei seniler Demenz. *Monatsschr Psychiatr Neurol* 1907; 22: 361–72.
9 Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. *Zeitschrift für die Gesamte Neurologie und Psychiatrie* 1911; 4: 356–85.
10 Berrios GE. Alzheimer's disease: a conceptual history. *Int J Geriatr Psychiatry* 1987; 5: 355–65.
11 Beach TG. The history of Alzheimer's disease: three debates. *J Hist Med Allied Sci* 1987; 42: 327–49.
12 Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). II: standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991; 41: 475-76

1910

BIR ALMAN NÖRO PSIKIYATRISTI EMIL KRAEPELIN HASTALIğI
ALZHEIMER HASTALIğI OLARAK ADLANDIRDI VE
“IN THE EIGHTH EDITION OF HIS BOOK PSYCHIATRIE”
KITABINDA YAYINLADI.

1931

ELEKTRON MIKROSKOBU BEYNI INCELEMEYE BAşLIYOR.
1931’TE IKI ALMAN BILIM ADAMI MAX KROLL VE ERNST
RUSKA’NIN ORTAK CALIsMASI SONUCUNDA ELEKTRON

1968

KOGNITIF ÖLÇÜM SKALALARI GELIŞTIRILIYOR.

BIMC

Initial Evaluation of the Patient with Suspected Dementia

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Dementia is a common disorder among older persons, and projections indicate that the number of patients with dementia in the United States will continue to grow. Alzheimer's disease and vascular dementia account for the majority of cases of dementia. After a thorough history and physical examination, including a discussion with other family members, a baseline measurement of cognitive function should be obtained. The Mini-Mental State Examination is the most commonly used instrument to document cognitive impairment. Initial laboratory evaluation includes tests for thyroid-stimulating hormone and vitamin B_{12} levels. Structural neuroimaging with noncontrast computed tomography or magnetic resonance imaging also is recommended. Other testing should be guided by the history and physical examination. Neuropsychologic testing can help determine the extent of cognitive impairment, but it is not recommended on a routine basis. Neuropsychologic testing may be most helpful in situations where screening tests are normal or equivocal, but there remains a high level of concern that the person may be cognitively impaired. (Am Fam Physician 2005;71:1745-50. Copyright© 2005 American Academy of Family Physicians.)

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). EB CME is clinical content presented with practice recommendations supported by evidence that has been systematically reviewed by an AAFP-approved source.

See page 1635 for strength-of-recommendation labels.

Dementia is a syndrome of gradual onset and continuing decline of higher cognitive functioning. It is a common disorder in older persons and becomes more prevalent in each decade of life. Approximately 10 percent of adults 65 years and older, and 50 percent of adults older than 90 years, have dementia. It is common for older patients to present to family physicians with concerns of memory loss. With an accurate and timely diagnosis of dementia, appropriate therapies can be initiated to reduce further cognitive decline. Therefore, family physicians play a key role in evaluating patients with suspected dementia. Given conflicting recommendations about the initial evaluation of patients with dementia, the availability of genetic markers for Alzheimer's disease, and new neuroimaging methods such as positron emission tomography, confusion may arise concerning how best to evaluate these patients.[1-6] This article reviews the evidence regarding the initial evaluation of the patient who presents with memory loss.

Signs and Symptoms of Dementia

Patients often present with concerns of recent memory loss. However, it is not uncommon for a family member to bring these concerns to the physician because some patients deny their impairment or excuse the memory loss as a normal part of aging. The diagnosis of dementia can be suggested when there is an impairment in memory and an impairment of at least one other area of higher cognitive functioning (e.g., judgment, abstract thinking, complex task performance, agnosia, apraxia, visuospatial awareness, personality change in the context of deficits) that interferes with normal social and executive functioning in an otherwise alert person.[7]

Early symptoms that may suggest a dementing illness include difficulty in learning and retaining new information, handling complex tasks, reasoning (for otherwise simple problem-solving), and problems with spatial awareness (finding one's way around familiar places), language (specifically difficulty expressing oneself or getting "lost" in conversations), and behavior (usually passive, suspicious, or more irritable or aggressive than usual).[8]

Differential Diagnosis

Alzheimer's disease accounts for 50 to 60 percent of all dementing illnesses. Vascular dementias (e.g., major cerebrovascular

Summary of Recommendations

Key clinical recommendation	*Label*	*References*
Physicians should measure the patient's cognitive impairment using a test that they are familiar with and adept in, such as the Mini-Mental State Examination.	C	3
Initial laboratory evaluation, including tests for complete blood count, thyroid-stimulating hormone, serum electrolytes, serum calcium, and serum glucose, should be performed.	C	3
Structural neuroimaging (noncontrast computed tomography or magnetic resonance imaging) should be performed.	C	3
Referral for neuropsychologic testing cannot be recommended on a routine basis.	C	13, 16
A thorough history should include discussion with other family members and evaluation of the patient for depression. The Geriatric Depression Scale is an example of an instrument that can be used.	C	17

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 1635 for more information.

insults, microvascular pathology) are common in 15 to 20 percent of patients, and often occur with Alzheimer's disease. The combination of Alzheimer's disease and vascular dementia or other dementing disorders is termed "mixed dementias." Conditions that may cause dementia are listed by frequency in *Table 1*.[6,8] Less than 10 percent of dementias are caused by treatable conditions ("reversible dementia"). Because depression, vitamin B_{12} deficiency, and hypothyroidism often are comorbid conditions, it is not uncommon to treat an apparently reversible dementia only to find that symptoms were really caused by Alzheimer's disease or vascular dementia.

Early symptoms of dementia may include difficulty in learning new infomation, handling complex tasks, reasoning, spatial awareness, language, and behavior.

Mental Status Examinations

Mental status examinations are used to measure the degree of cognitive impairment. A number of instruments have been developed for this purpose. Five commonly used instruments and their characteristics are shown in *Table 2*.[9] These instruments measure performance in similar areas of cognitive function and take five to 10 minutes to administer and score. Each is reliable for ruling out dementia when results are negative.

MINI-MENTAL STATE EXAMINATION

The most frequently used mental state examination in North America is the Mini-Mental State Examination (MMSE). The MMSE measures many areas of cognitive functioning including memory, orientation to place and time, naming, reading, copying (visuospatial orientation), writing, and the ability to follow a three-stage command. It can be administered in five to 10 minutes and is scored from zero to 30 points. A score of fewer than 24 points signifies cognitive impairment, although the test can be adjusted for educational level.[10] The MMSE is more specific but less sensitive (i.e., gives more false negatives but fewer false positives) in highly educated individuals. It is available online at http://www.minimental.com and http://www.aafp.org/afp/20010215/703.html.

BLESSED INFORMATION MEMORY CONCENTRATION

The Blessed Information Memory Concentration (BIMC) instrument primarily assesses orientation, memory, and concentration (counting forward and backward, and naming the months of the year in reverse order).[11] Errors are counted and can total from zero to 28. Making more than 10 errors indicates cognitive impairment.

1968

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BIMC

TABLE 1
Frequency of Common Causes of Dementia

Cause	Frequency (%)
Alzheimer's disease	50 to 60
Vascular disease	15 to 20
Mixed dementia	10 to 20
Other	< 10
Diffuse Lewy-Body dementia	
Frontotemporal dementia (Pick's disease)	
Parkinson's disease	
Alcohol-related dementia	
Huntington's disease	
Prion disease (Jacob-Creutzfeldt disease/slow virus)	
Trauma (subdural hematoma)	
Infections (syphilis, acquired immunodeficiency syndrome, opportunistic infections)	
Encephalitis	
Hypothyroidism	
Vitamin B_{12} deficiency	
Depression	

Information from references 6 and 8.

BLESSED ORIENTATION MEMORY CONCENTRATION

The Blessed Orientation Memory Concentration instrument is a shortened version of the BIMC with six questions assessing orientation to time, recall of a short phrase, counting backward, and reciting the months in reverse order.[12] A weighted score of errors is calculated. As with the BIMC, making more than 10 errors is indicative of cognitive impairment.

SHORT TEST OF MENTAL STATUS

The Short Test of Mental Status (STMS) assesses orientation, attention, recall, calculation, abstraction, clock drawing, and copying. The STMS has a total score of 38. A score of 29 or lower indicates impaired cognitive function.

FUNCTIONAL ACTIVITIES QUESTIONNAIRE

Although it is not a mental status examination, the Functional Activities Questionnaire (FAQ) measures functional activities that may be impaired by dementia (e.g., ability to shop, cook, pay bills).[13] The FAQ is answered by a family member or friend who knows and has observed the patient. The "informant" is asked to rate the performance of the patient in 10 activities as someone who is dependent, requires assistance, or has difficulty but does independently. Scores range from zero to 30 with a cutoff of 9 (i.e., dependent in three or more activities) signifying impairment. This information may be useful in a clinical context, but the patient's cognitive function still needs to be evaluated.

TABLE 2
Commonly Used Instruments to Evaluate Mental Status

Instrument	Sensitivity (%)	Specificity (%)	Positive predictive value (%)*	Negative predictive value (%)†
Mini-Mental State Examination	71 to 92	56 to 96	15 to 72	95 to 99
Blessed Information Memory Concentration	90	65 to 90	22 to 50	98 to 99
Blessed Orientation Memory Concentration	69	90	43	96
Short Test of Mental Status	81	90	47	98
Functional Activity Questionnaire	90	90	50	90

**—Percentage of persons who have dementia and an abnormal test.*

†—Percentage of persons who do not have dementia and have a normal test.

Adapted with permission from Boustani M, Peterson B, Hanson L, Harris R, Lohr KN. Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2003;138:930.

It is not uncommon to treat a presumptively "reversible dementia" only to find that the real cause is Alzheimer's disease or vascular dementia.

Initial Laboratory Evaluation

The purpose of laboratory testing is to exclude potentially reversible causes of dementia. The American Academy of Neurology recommends two laboratory tests for the initial evaluation of the patient with suspected dementia—thyroid function and vitamin B_{12} level.[3] The Second Canadian Consensus Conference on Dementia (CCCD) recommends obtaining results for complete blood cell count, thyroid-stimulating hormone level, serum electrolytes, serum calcium, and serum glucose to exclude potential infections or metabolic causes for cognitive impairment.[1] Other testing, such as serology for syphilis, Lyme disease titer, human immunodeficiency virus (HIV), urinalysis, culture and sensitivity, heavy metal assays, erythrocyte sedimentation rate, liver function, serum folic acid level, or other vitamin level assays should be performed only when clinical suspicion warrants.

A lumbar puncture is not recommended for routine evaluation, but should be considered for patients with suspected neurosyphilis, cerebral vasculitis, HIV infection, slow-virus diseases, or cerebral Lyme disease. Routine testing for genetic markers such as apolipoprotein E is not recommended.

Imaging Studies

Neuroimaging may diagnose vascular disease, normal pressure hydrocephalus, tumors, abscess, or subdural hematoma. However, the yield from neuroimaging in identifying a potentially reversible cause of dementia is low.[3] Therefore, there is some controversy regarding the routine use of neuroimaging in the primary evaluation of dementia. The CCCD recommends the following criteria for neuroimaging: age younger than 60 years, atypical or rapid cognitive decline, recent head trauma, localized neurologic signs or symptoms, gait disturbance, urinary incontinence (early in the course of the dementia), use of anticoagulants, and history of cancer.[1] The American Academy of Neurology recommends that all patients have a magnetic resonance imaging study or noncontrast computed tomography as part of the initial evaluation.[3] The American College of Radiology recommends magnetic resonance imaging as the preferred study if one is chosen.[5]

Routine use of single photon emission computed tomography or positron emission tomography is not recommended by evidence-based guidelines or most experts.[1-5,8,10,12,14-16] Electroencephalography is indicated only if "slow-virus" or prion disease is suspected.

Neuropsychologic Testing

Neuropsychologic testing can comprehensively assess multiple domains of higher cognitive functioning including intelligence and behavioral functioning. A trained psychologist or psychometrician performs neuropsychologic testing. Higher cognitive functioning (logical reasoning, abstract and conceptual reasoning, visuospatial orientation, constructional ability, abstract thinking, memory, verbal reasoning, verbal fluency, etc.) is evaluated. Neuropsychologic testing has the potential to identify cognitive impairment objectively in patients with higher baseline cognitive abilities. It also may reveal subtle cognitive impairment in persons with

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suspected cognitive impairment or dementia and in persons at increased risk of cognitive impairment,[17] and may be useful in distinguishing patients with mild cognitive impairment from those with dementia.

Neuropsychologic testing may be considered as an adjunctive option for patients and families who are anxious to define and measure (in a standardized fashion) cognitive functioning and then monitor for changes over time. Other candidates for possible formal testing include persons who are not well educated, those who do not have English as their native language, and persons who are functioning "normally" or who are minimally impaired on screening. Although it can be useful in evaluating the impact of depression, anxiety, and other psychologic symptoms on cognitive functioning,[13] neuropsychologic testing is not recommended routinely for all patients with suspected dementia.

Evaluation

An algorithm to guide the initial evaluation of the patient with dementia is shown in *Figure 1*. In the majority of patients, a thorough history and physical examination

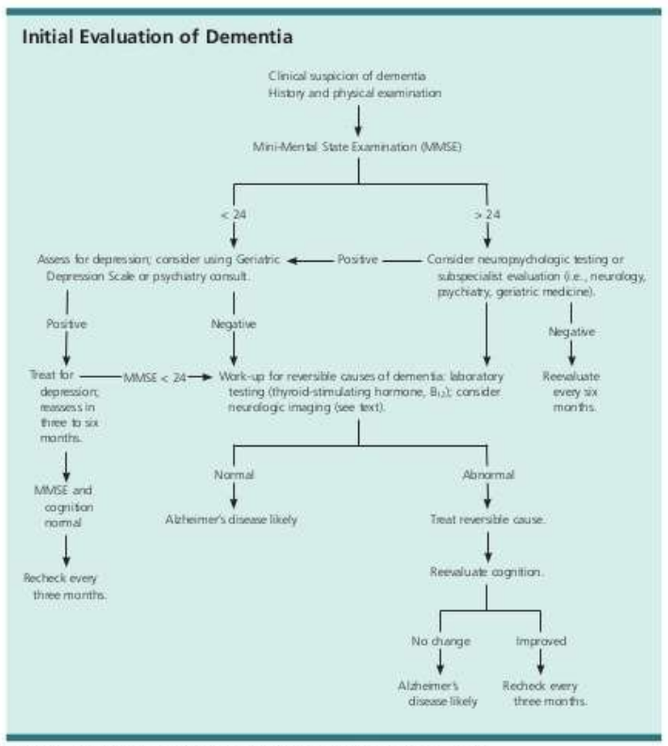

Figure 1. Algorithm for initial evaluation of the patient with dementia.

will identify the most likely cause of cognitive decline. Although relatively uncommon, potentially treatable causes of dementia can be ruled out by further laboratory testing and neuroimaging. In many patients, reversible conditions such as hypothyroidism or depression are comorbid rather than being the actual cause of cognitive decline.

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REFERENCES

1. Chertkow H, Bergman H, Schipper HM, Gauthier S, Bouchard R, Fontaine S, et al. Assessment of suspected dementia. Can J Neurol Sci 2001;28(suppl 1):S28-41.
2. Kawas CH. Clinical practice. Early Alzheimer's disease. N Engl J Med 2003;349:1056-63.
3. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Neurology 2001;56:1143-53.
4. Santacruz KS, Swagerty D. Early diagnosis of dementia. Am Fam Physician 2001;63:703-13,717-8.
5. Braffman B, Drayer BP, Anderson RE, Davis PC, Deck MD, Hasso AN, et al. Dementia. Radiology 2000;215(suppl):525-33.
6. Leifer BP. Early diagnosis of Alzheimer's disease: clinical and economic benefits. J Am Geriatr Soc 2003;51 (5 suppl Dementia):S281-8.
7. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, D.C.: American Psychiatric Association, 2000.
8. Friedland RP, Wilcock GK. Dementia. In: Evans JG, Williams TF, Beattie BL, Michel JP, Wilcock GK, eds. Oxford textbook of geriatric medicine. 2d ed. Oxford: Oxford University Press, 2000:922-32.
9. Boustani M, Peterson B, Hanson L, Harris R, Lohr KN. Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2003;138:927-37.
10. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386-91.
11. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797-811.
12. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Shimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry 1983;140:734-9.
13. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol 1982;37:323-9.
14. Chui H, Zhang Q. Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. Neurology 1997;49:925-35.
15. Agency for Health Care Policy and Research. Early identification of Alzheimer's disease and related dementias. Clin Pract Guidel Quick Ref Guide Clin 1996;(19):1-28.
16. Geldmacher DS, Whitehouse PJ. Evaluation of dementia. N Engl J Med 1996;335:330-6.
17. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Neurology 2001;56:1133-42.

1970-1979: modern araştirma alanlari

1974

"Founding of National Institute on Aging"
(NIA) ve (NIH) kurularak çalişma yapmaya başliyor

1976

nörolog Robert Katzman tarafindan Alzheimer en sik görülen demans tipi olarak taninmaya başliyor.

Archives of Neurology de yayinlaniyor.

Editorial

The Prevalence and Malignancy of Alzheimer Disease

A Major Killer

An accompanying letter to the editor (p 304) provides another illustration of the malignancy of Alzheimer disease, a phenomenon well known to neurologists. Katzman and Karasu[1] estimate that the senile form of Alzheimer disease may rank as the fourth or fifth most common cause of death in the United States. Yet the US vital statistics tables do not list "Alzheimer disease," "senile dementia," or "senility" as a cause of death, even in the extended list of 263 causes of death.

The argument that Alzheimer disease is a major killer rests on the assumption that Alzheimer disease and senile dementia are a single process and should, therefore, be considered a single disease. Both Alzheimer disease and senile dementia are progressive dementias with similar changes in mental and neurological status that are indistinguishable by careful clinical analyses.[2,3] The pathological findings are identical—atrophy of the brain, marked loss of neurons, neurofibrillary tangles, granulovacuolar changes, and neuritic (senile) plaques. Ultrastructural studies have established the identity of the neurofibrillary tangle with its twisted tubule and the senile plaque with its amyloid core and degenerating neurites in the brains of patients with Alzheimer disease (under age 65) and senile dementia (over age 65). Most recent ultrastructural and neurochemical studies indicate that the neurofibrillary tangle in both disorders is characterized by the twisted tubule that represents two neurofilaments joined together in a helical fashion with a period of 800 Angstroms. The studies of Tomlinson et al[4] and Blessed et al[5] have established a quantitative correlation between the degree of dementia and the number of neurofibrillary tangles and senile plaques in the cerebral cortex. The evidence on which a distinction between senile dementia and Alzheimer disease can still be argued is the genetic analysis of Larsson et al.[6] In their analysis of the kindred of patients with senile dementia, numerous relatives were found with senile dementia, but none with a diagnosis of Alzheimer disease. However, the incidence of the Alzheimer senile dementia complex is strongly age-related, even among the elderly. Larsson et al[6] had suggested a predisposing, autosomal dominant gene with age-related penetrance, reaching a penetrance of 40% at age 90. Therefore, the absence of any relative with "Alzheimer disease" might be related to its relative infrequency in patients under 65. Moreover, in a genetic study carried out in Switzerland, Constantinidis et al[7] encountered the two diseases in the same family. Although further studies are clearly indicated, the fact remains that neither the clinician, the neuropathologist, nor the electron microscopist can distinguish between the two disorders, except by the age of the patient. Today, the majority of workers in the field accept the identity of the two disease.[8] We believe that it is time to drop the arbitrary age distinction and adopt the single designation, Alzheimer disease.

Precise epidemiological information is not available concerning the prevalence of Alzheimer disease in the United States. However, several excellent community surveys of the prevalence of organic dementias in persons over age 65 have been carried out in northern Europe.[9-15] In these series, care has been taken to include persons living at home as well as those receiving institutional care. The prevalence of "severe dementia" or organic "psychosis," terms used to describe patients in whom, in addition to intellectual deterioration, there was evidence of disorganization of the personality and inability to carry out the normal tasks of daily living, averaged 4.1%. The prevalence of "mild dementia" and "mild mental deterioration" or "chronic brain syndrome without psychosis," terms used to describe individuals with intellectual impairment who are still able to carry out activities of daily living, averaged 10.8%. Estimates of the incidence of Alzheimer disease (senile dementia) among patients over age 65 with organic dementia vary between 40%[16] and 58%.[4] Applying these figures to the United States, the prevalence of Alzheimer disease in persons

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1980:
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DR STONE BAŞKAN OLDU. BUGÜN 2100 PROJEDEN $300
ILYON KAZANDI VE BIRÇOK ÇALIŞMAYA DESTEK OLDU

TÜRKIYE ALZHEIMER DERNEĞİ, ALZHEIMER HASTALIĞI VE DIĞER DEMANS SENDROMLARIYLA ILGILENEN SAĞLIK PERSONELI, HASTALAR, HASTA YAKINLARI VE GÖNÜLLÜLER TARAFINDAN 1997 YILINDA KURULMUŞTUR.

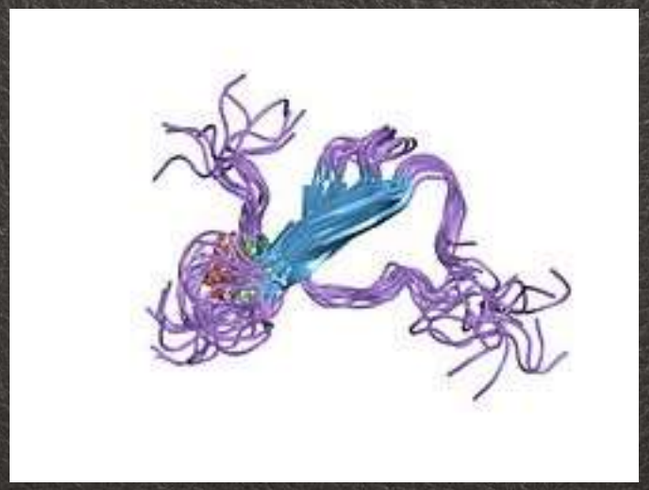
ESKIŞEHIR ALZHEIMER DERNEĞI 2001 YILINDA KURULDU.

1983
aylik ulusal Alzheimer hastaliği deklarasyonu çikmaya başlandi.farkindalik artti ve 1983 de ilk ulusal kongre yapildi.

1984
Beta-amiloyid bulundu.

George Glenner ve Cai'ne Wong, beta amiloid olarak da bilinen ''a novel cerebrovascular amyloid protein'' yayinladi.

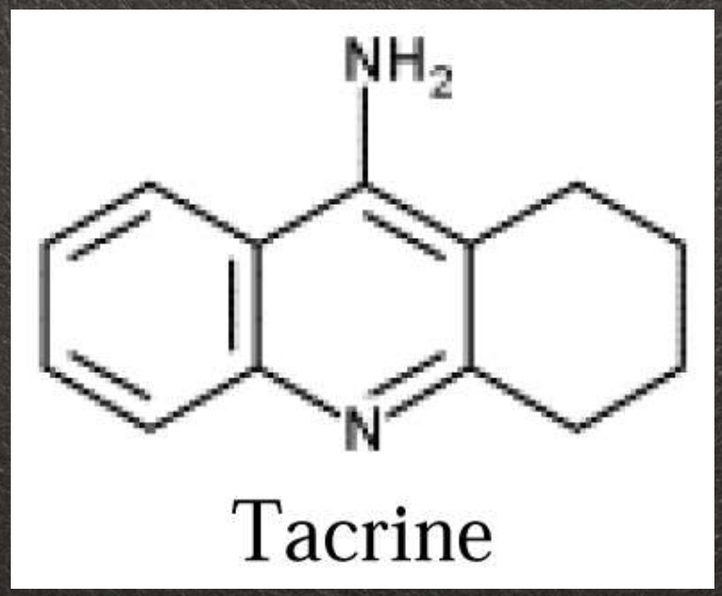
1986
Tau protein bulundu.



1987

ILK ALZHEIMER ILACI BULUNDU

"The Alzheimer's Association", NIA ve Warner-Lambert Pharmaceutical Company (Pfizer) destekladi ve takrin klinik çalişmalari yayinlandi.



Tacrine

Tacrine for Treating Alzheimer's Disease

Gary W. Small, MD

JAMA. 1992;268(18):

Article

References

ABSTRACT

ABSTRACT | REFERENCES

Tacrine (tetrahydroaminoacridine, THA) was first available in Australia in the mid 1940s when it was used with morphine to lessen respiratory depression without affecting analgesia.1 Its anticholinesterase activity eventually led to clinical trials in patients with presumptive Alzheimer's disease (AD), but these pilot studies demonstrated only modest efficacy using tacrine alone or in combination with lecithin. Consistent findings of a cholinergic deficit in AD make such cholinergic manipulation a theoretically attractive palliative treatment. Trials of other cholinomimetics, however, had shown at best modest results and often practical limitations—eg, choline causes a fishy skin odor and the 30-minute half-life of physostigmine is too brief for lasting clinical effects. Scientific and public interest, as well as controversy, exploded in 1986 when Summers and colleagues reported dramatic results from a double-blind, placebo-controlled trial of tacrine in 17 patients with apparent clinical diagnoses of AD.

CNS Drugs 4 (3): 168-181, 1995
1172-7047/95/0009-0168/$07.00/0

Tacrine-Induced Hepatotoxicity
Tolerability and Management

Ross Balson,[1] *Peter R. Gibson*,[1,2] *David Ames*[3] and *Prithi S. Bhathal*[4]

1 Department of Gastroenterology, The Royal Melbourne Hospital, Parkville, Victoria, Australia
2 University of Melbourne Department of Medicine, The Royal Melbourne Hospital, Parkville, Victoria, Australia
3 University of Melbourne Department of Psychiatry, The Royal Melbourne Hospital, Parkville, Victoria, Australia
4 Department of Anatomical Pathology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

Contents

Summary

Tacrine, a centrally acting, reversible acetylcholinesterase inhibitor, is effective in the treatment of Alzheimer's disease. However, a major adverse effect of the drug is hepatotoxicity, which affects about one-half of patients treated.

The pathogenic mechanisms of this hepatotoxicity are poorly understood, but probably involve reactive metabolites. The liver injury is predominantly that of hepatocellular necrosis, and manifests as an increase in serum alanine aminotransferase (ALT) levels; 25 and 2% of patients will experience ALT levels greater than 3 times and 20 times the upper limit of the normal range, respectively.

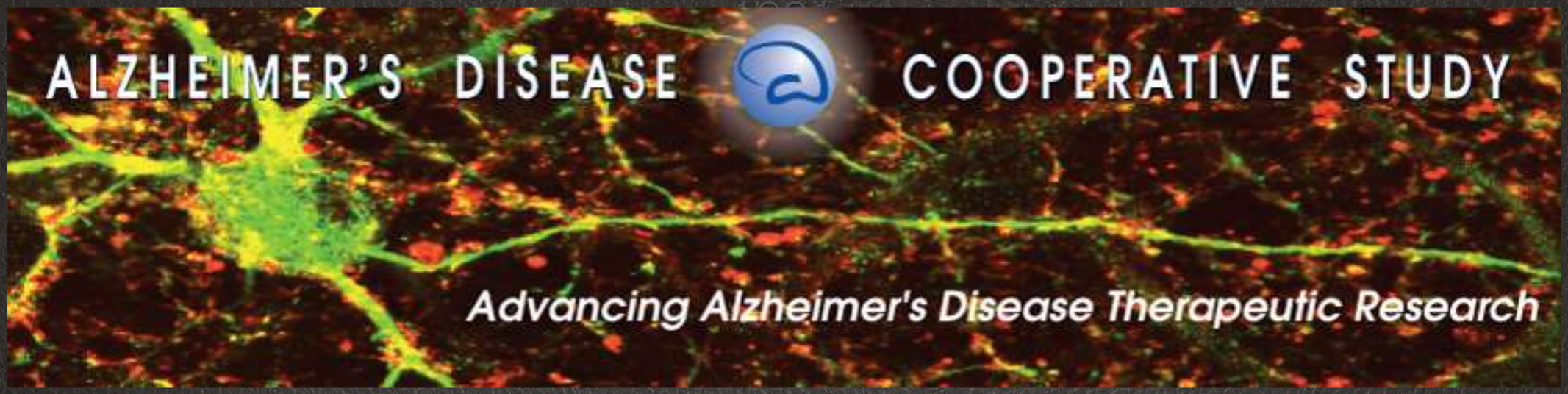
Although hepatotoxicity is generally asymptomatic and has not led to death, severe reactions have been reported, and careful monitoring of ALT levels is mandatory in all patients, especially during initiation of therapy and following

1987

ILK ALZHEIMER GENI BULUNDU

KROMOZOM 21 ÜZERINDE SAPTANAN BIR GEN APP KODLANMASINDAN SORUMLU IDI.

1990-1999: TEDAVI ACILIYETI



ADCS, 30 araştirmayi içeriyordu (23 ilaç çalişmasi ve 7 enstruman gelişTirme). tüm çalişmalar 9-800 arasi hastayi içeriyordu. ADCS çok sayida yayin oldu.

1990-1999: TEDAVI ACILIYETI

1993

ILK ALZHEIMER RISK FAKTÖR GENI ORTAYA ÇIKTI
APOE-ε4, KROMOZOM 19 ILE ILGILI

1993

FDA ILK ALZHEIMER ILACINI ONADI.
TACRINE (COGNEX)

1994

ILK DÜNYA ALZHEIMER GÜNÜ (21 EYLÜL)

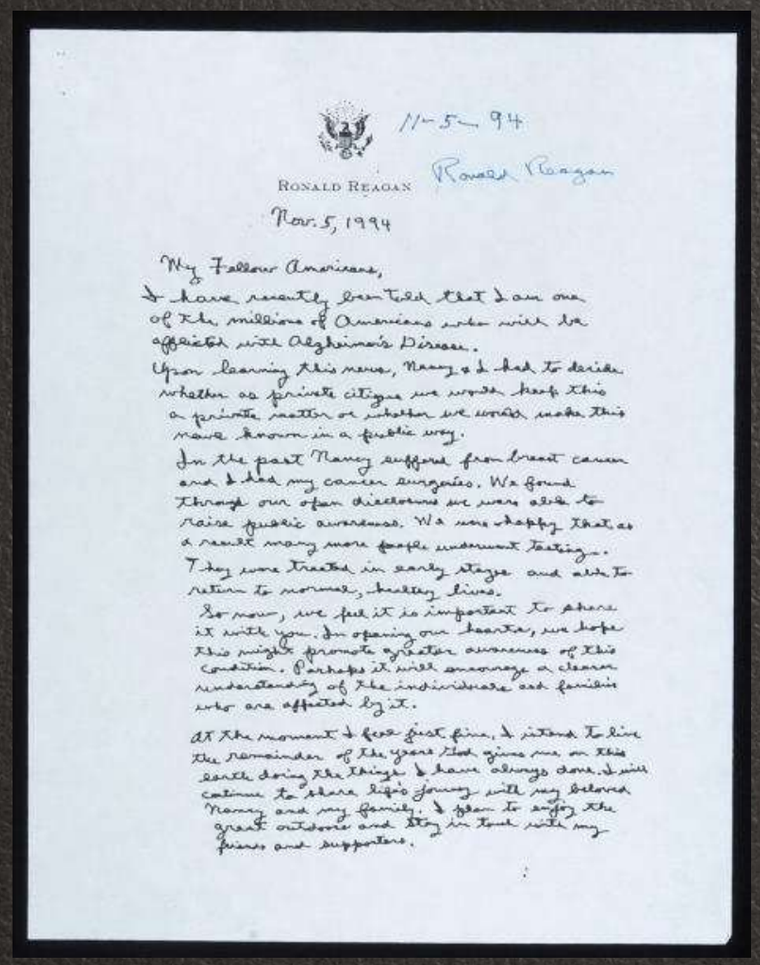
1995

İLK TRANSJENIK FARE MODEL AÇIKLAMASI

1999

"ALZHEIMER AŞISI" BAŞLANDI

1994: BAŞKAN REAGAN TANISI DUYURULDU



11-5-94

Ronald Reagan

Nov. 5, 1994

My Fellow Americans,

I have recently been told that I am one of the millions of Americans who will be afflicted with Alzheimer's Disease.

Upon learning this news, Nancy & I had to decide whether as private citizens we would keep this a private matter or whether we would make this news known in a public way.

In the past Nancy suffered from breast cancer and I had my cancer surgeries. We found through our open discussions we were able to raise public awareness. We were happy that as a result many more people underwent testing. They were treated in early stages and able to return to normal, healthy lives.

So now, we feel it is important to share it with you. In opening our hearts, we hope this might promote a greater awareness of this condition. Perhaps it will encourage a clearer understanding of the individuals and families who are affected by it.

At the moment I feel just fine. I intend to live the remainder of the years God gives me on this earth doing the things I have always done. I will continue to share life's journey with my beloved Nancy and my family. I plan to enjoy the great outdoors and stay in touch with my friends and supporters.

Sevgili Amerikalilar,

Geçenlerde bana Alzheimer hastaliği ile tutulmuş olacak milyonlarca Amerikalinin biri olduğumu söylendi.

Şu anda, ben sadece kendimi iyi hissediyorum. Ben sevgili Nancy ve ailemle birlikte hayat yolculuğunu paylaşmaya devam edeceğim.

Kapanişta, bana başkan olarak hizmet sağlayan bir büyük onur verdiğiniz için size, Amerikan halkina teşekkür ederim.
Şimdi hayatimin gün batimina doğru beni götürecek yolculuk başliyor. Ben Amerika için hep önde parlak bir şafak olacağini biliyorum.

Teşekkürler arkadaşlar.

İçtenlikle,

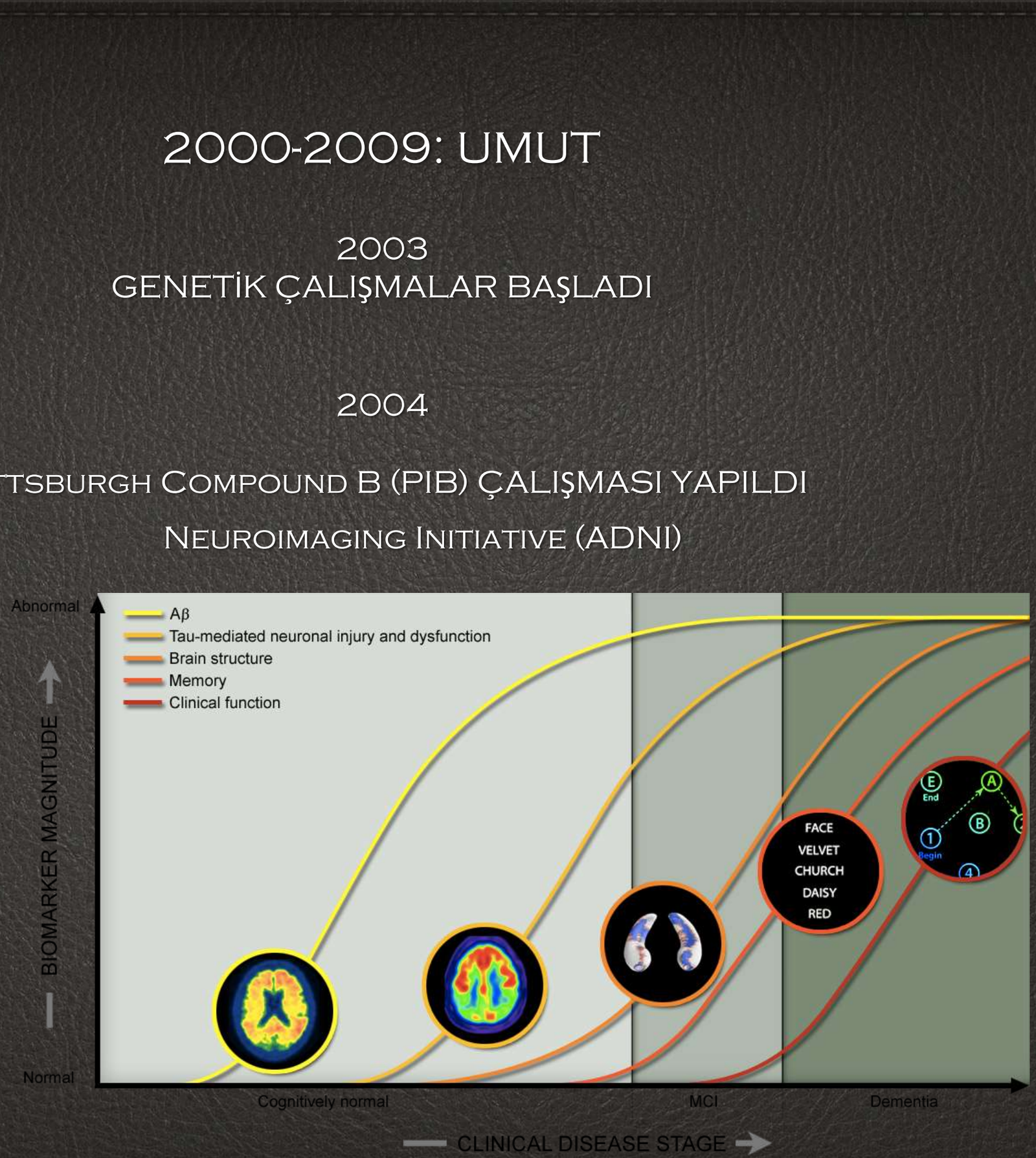
2000-2009: UMUT

2003
GENETİK ÇALIŞMALAR BAŞLADI

2004

PITTSBURGH COMPOUND B (PIB) ÇALIŞMASI YAPILDI

NEUROIMAGING INITIATIVE (ADNI)



2005

Alzheimer's & Dementia®

2008

ULUSLARARASI İLERİ ÇALIŞMALAR BAŞLADI

tional Society to Advance Alzheimer's Research and Treatment (ISTA

2009

KONGRE

r's Association International Conference on Alzheimer's Disease® (

BİYOMARKER STANDARDİZASYONU (BOS)

2010-2019 : ULUSAL VE ULUSLARARASI AJANDA

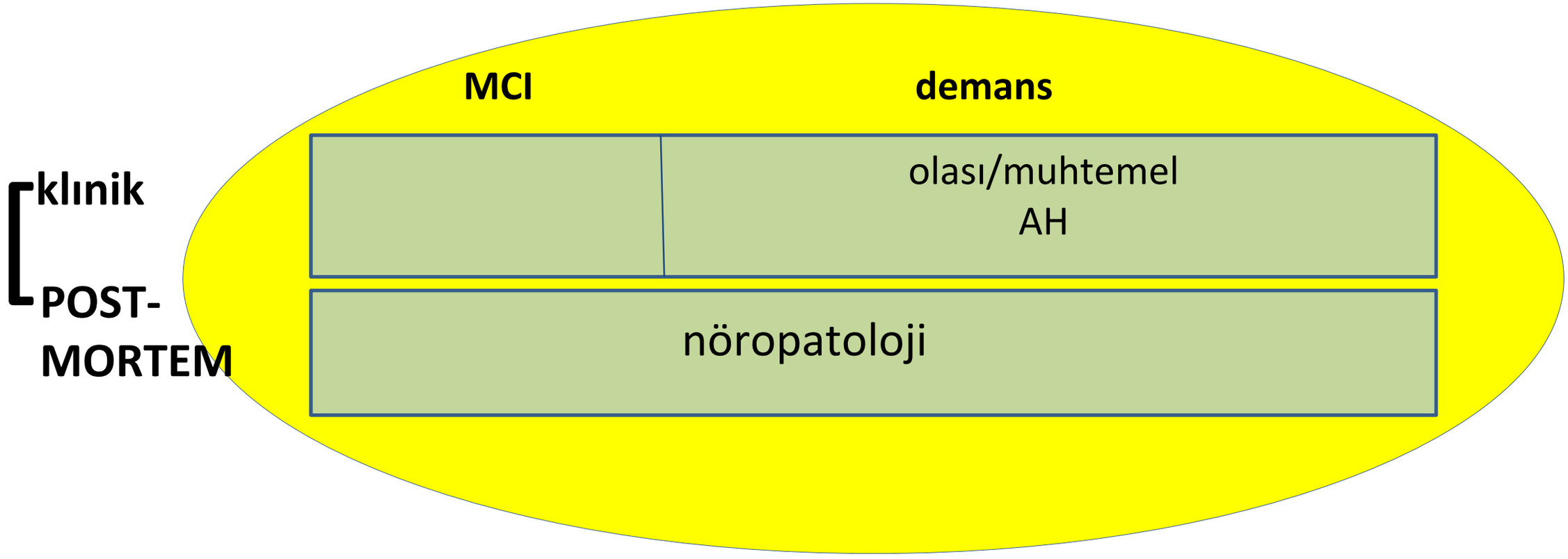
2010

"An influential model of biomarker changes during Alzheimer's disease progression is first published"

1984

NINCDS-ADRDA KRİTERLERİ

1) Alzheimer tanısı klinik ve patolojik bir tanıdır.
2) Tanı sadece olası ve muhtemel olarak verilir.
3) Hastalık ileri düzeyde ve demans eşik değerlerini aşmış ise kesin demans denilebilir.



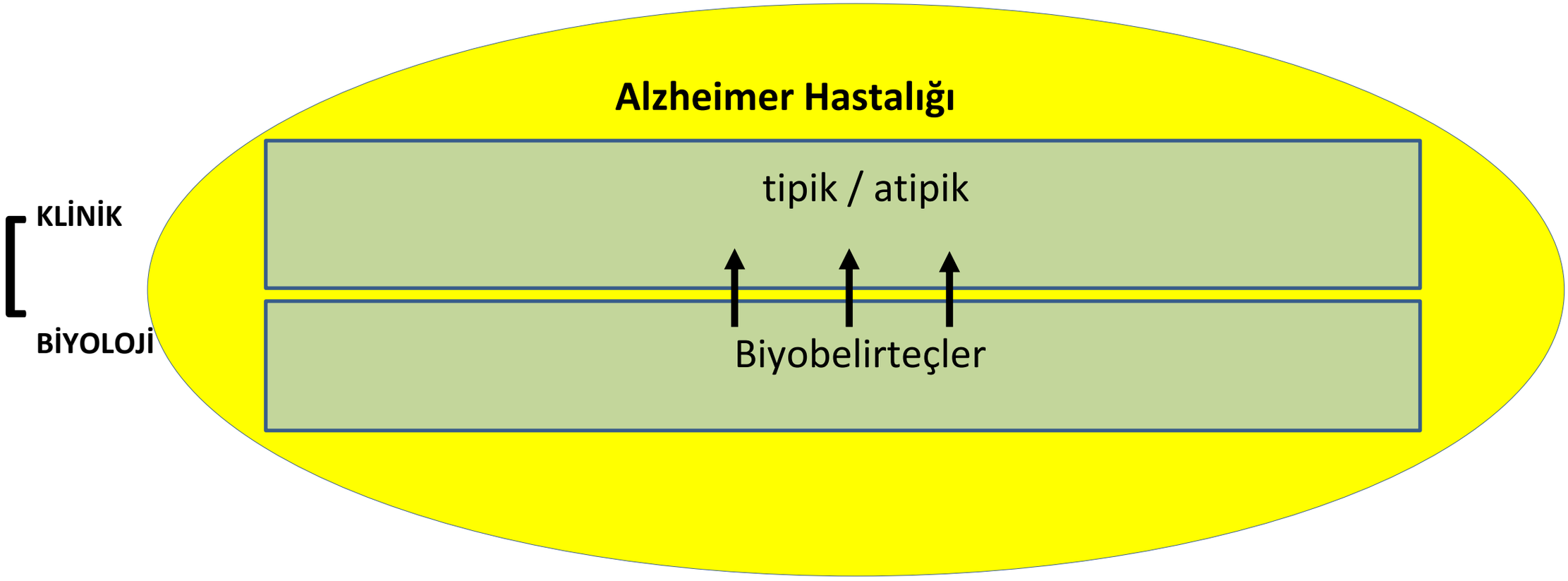
2010

yeni kurallar

KLINIK-BİYOLOJİK

Biyobelirteçler histopatolojinin göstergesidir.

→ klinik tanı invivo dur.
→ daha fazla referansa ihtiyaç yoktur.



2010-2019 : ULUSAL VE ULUSLARARARASI AJANDA

2011

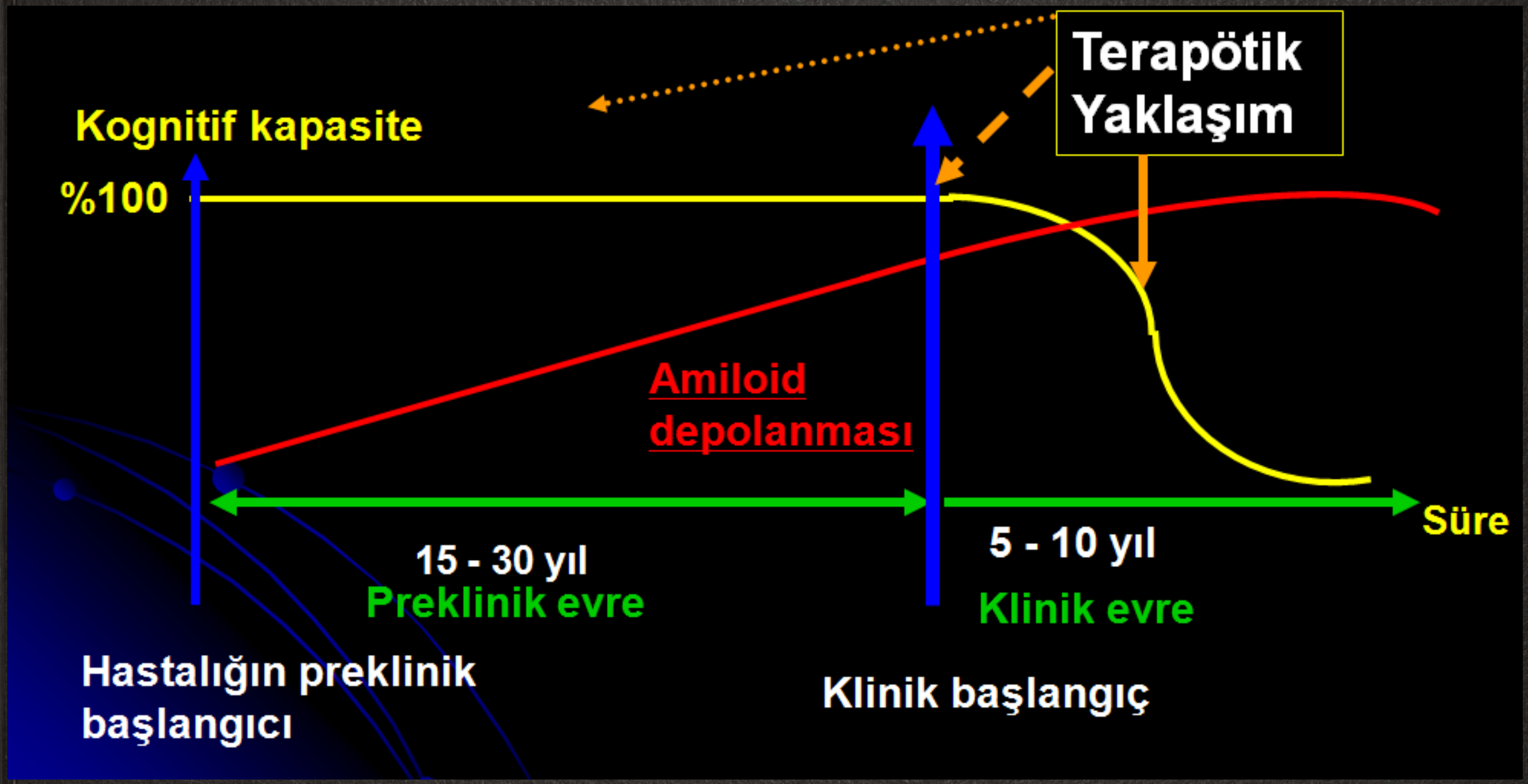
President Obama İMZALADI
ULUSAL Alzheimer PROJE HAREKETİ (NAPA)

ALZHEİMER HASTALIĞINDA YENİ KRİTERLER

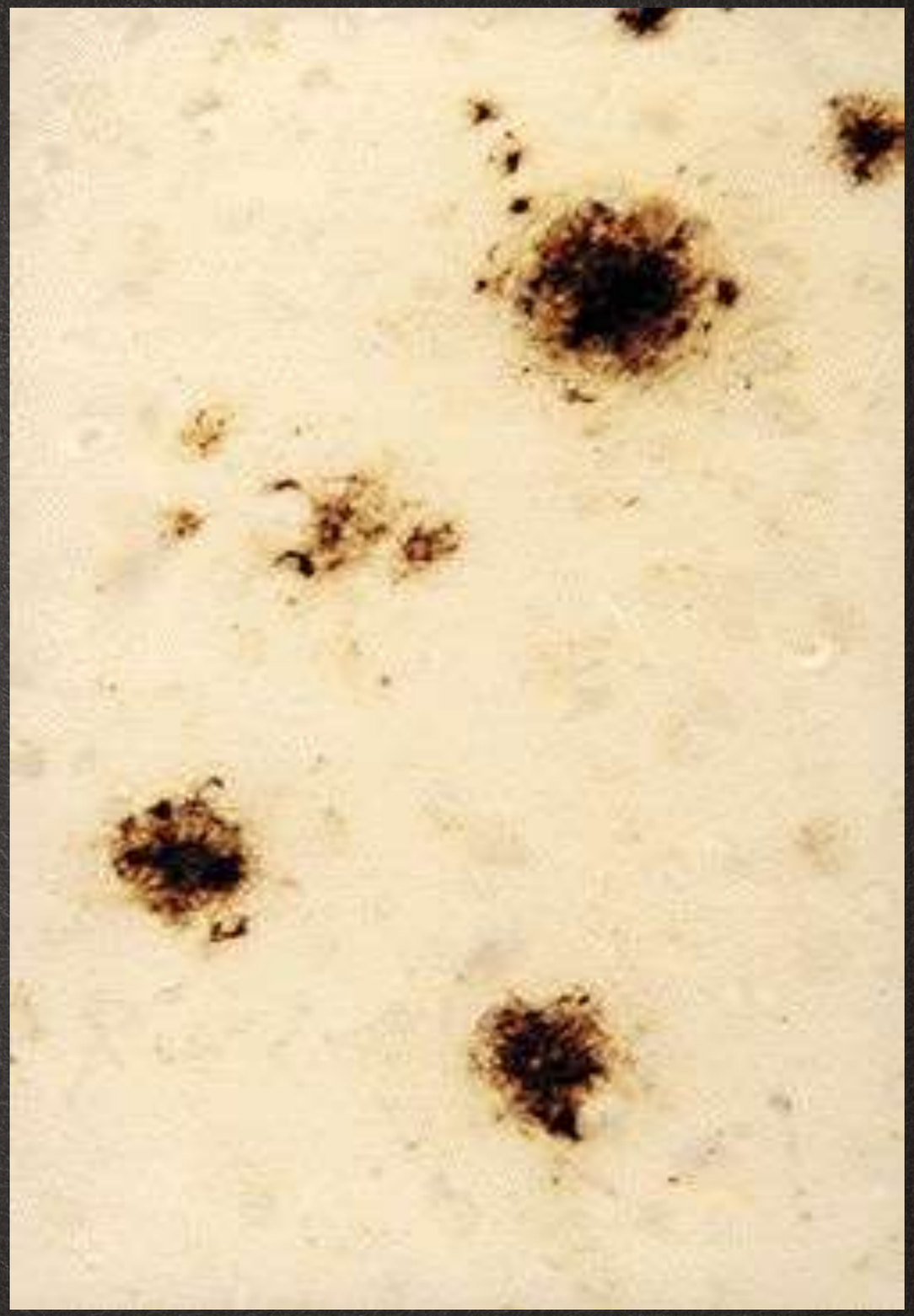
- 1906 Alzheimer tanımı
- 1970 Kolinerjik hipotez
- 1993 Takrin
- 1997 Vitamin E
- 1997 Donepezil
- 2000 Rivastigmine
- 2001 Galantamine
- 2003 Memantine
- 2008-2019 hastalık modifiye edici tedaviler

YENİ TANI KRİTERLERİ(2011)

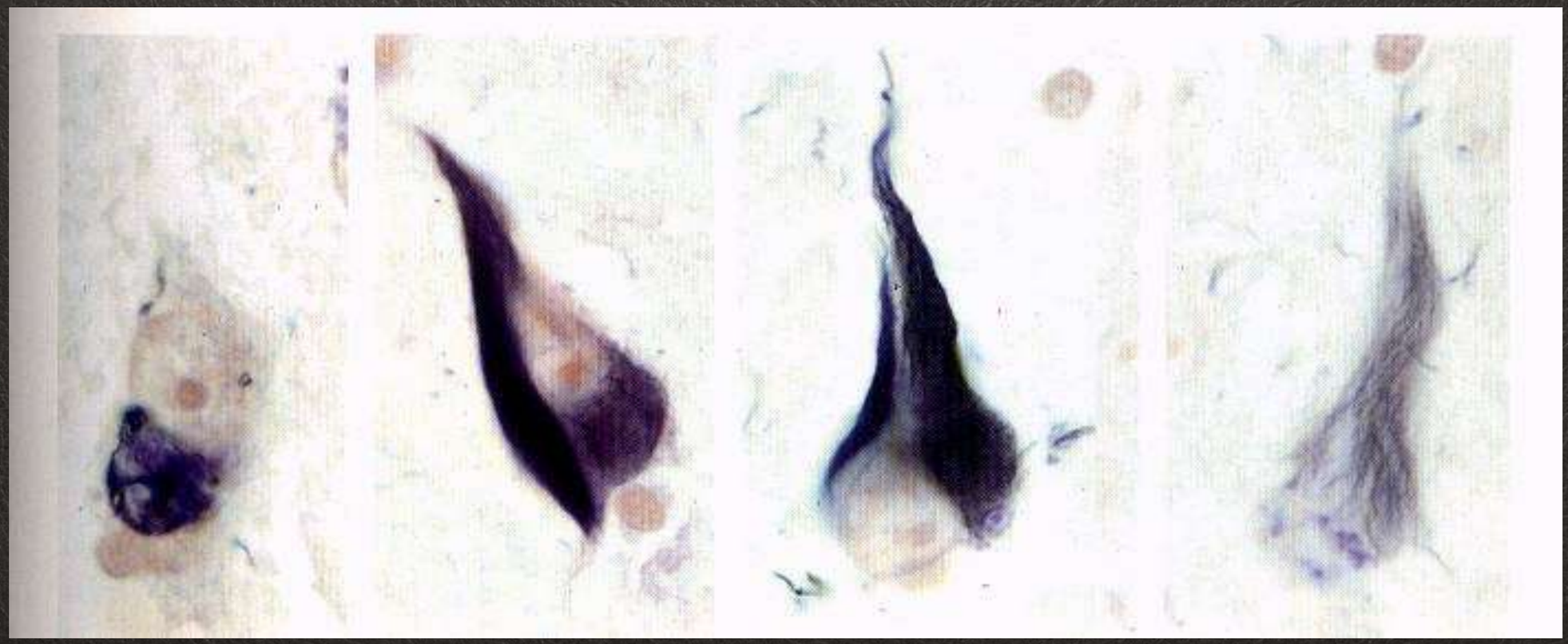
Stage 1: Dışarıdan normal
Stage 2: Çok hafif bozukluk
Stage 3: Hafif bozukluk
Stage 4: Orta dereceli bozukluk
Stage 5: Orta ciddi bozukluk
Stage 6: Ciddi bozukluk
Stage 7: Çok ciddi bozukluk


Terapötik
Yaklaşım
Kognitif kapasite
%100
Amiloid
depolanması
Süre
15 - 30 yıl
Preklinik evre
5 - 10 yıl
Klinik evre
Hastalığın preklinik
başlangıcı
Klinik başlangıç

AMİLOİD PLAK



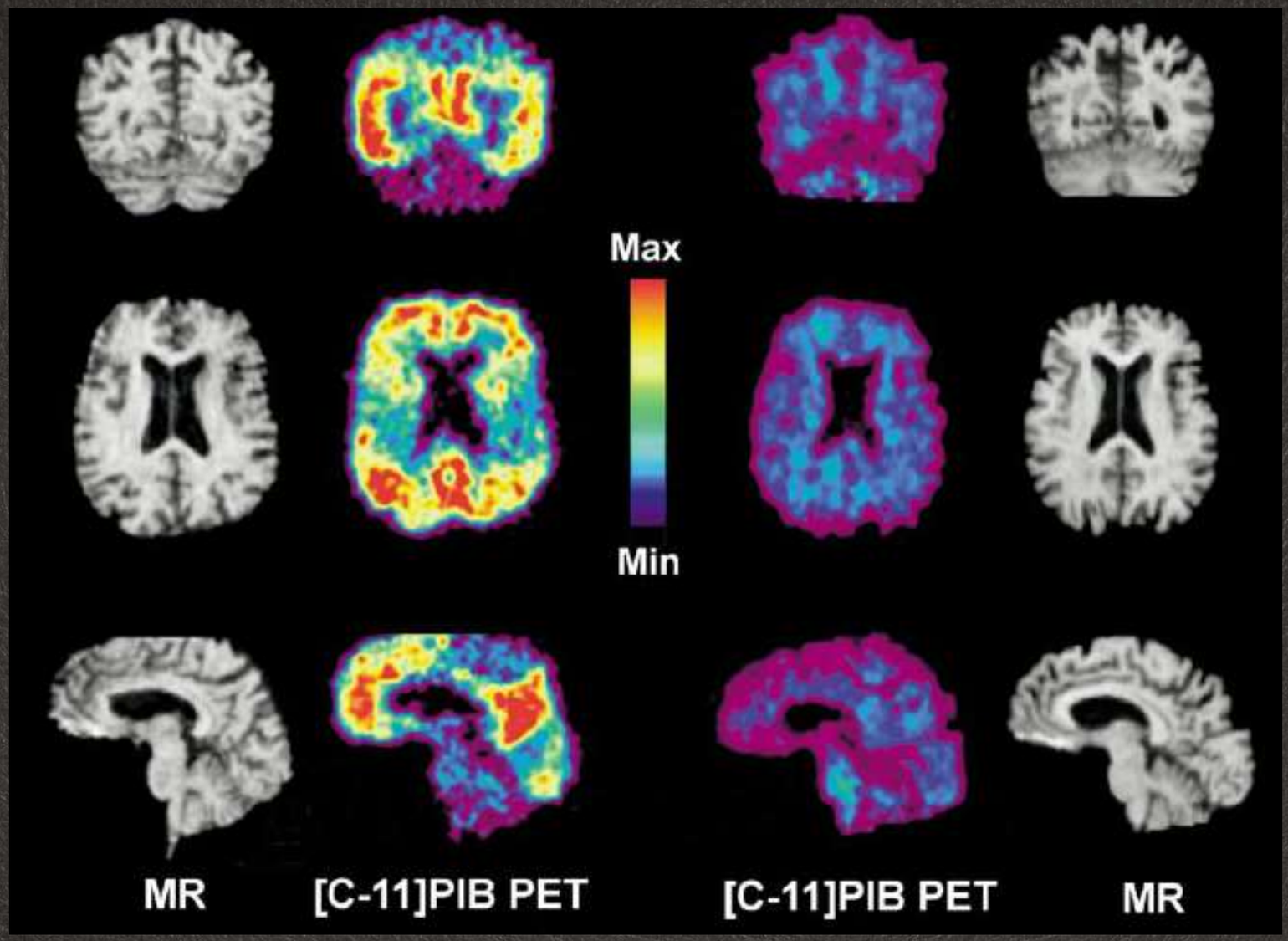
NÖROFİBRİLLER YUMAKLAR



	bellek	BOS	MRI	PET-FDG	PET-ligand
NINCDS - ADRDA	spesifik değildi	dışlama	dışlama	özgün değil	bilinmiyor
Yeni Kriterler	amnestik tip	↘ Abeta ↗ T- P tau	MTL atrofi	P–T hipometabolizma	PiB retansiyon
Prodromal AH için gerekenler	>%90 *Sarazin 2007*	>%90 *Hanson 2006*	>%85 *Colliot 2008*	>%80 *Mosconi 2004*	>%95 *Rowe 2007*

Sarazin et al. *Neurology.* 2007;69:1859-2016. Hansson et al. *Lancet Neurol*. 2006;5:228–234. Colliot et al. *Psychiatr Sci Hum Neurosci*. 2008;6:68-75. Mosconi et al. *Neurology*. 2004;63:2332-2340. Rowe et al. *Alzheimers Dement*. 2007;3.

PIB-PET İLE İLK ÇALIŞMA



16 AH ve 9 Normal. AH'lilerde %60-95 daha fazla tutulum. Bazı normaller AH gibi.

Klunk, Engler, Nordberg et al. Ann Neurol 2004

Saatlerden günlere yeniden tarama değişkenliği %5. Price 2005; Lopresti 2005

RİSK FAKTÖRLERİ

YAŞ

GENETİK

ERKEN BAŞLANGIÇ

GEÇ BAŞLANGIÇ

KADIN? ÖSTROJEN?

SİGARA

KAFA TRAVMASI

OBEZİTE

HİPERTANSİYON

SERUM KOLESTEROL YÜKSEKLİĞİ

SERUM HOMOSİSTEİN YÜKSEKLİĞİ

DEPRESYON

EĞİTİM VE ENTELLEKTÜEL KAYIP

KORUYUCU FAKTÖRLERİ

FİZİKSEL AKTİVİTE

KAHVE

ANTİOKSİDAN, VİT C, E, B6, B12

FOLAT

OMEGA 3 YAĞ ASİT ALIMI

2 DİL KONUŞMA

Primer koruma
Risk faktörlenin tanınması
İlerlemenin durdurulması

Sekonder koruma
İlerlemenin yavaşlatılması veya önlenmesi

İlerlemenin yavaşlatılması
Semptomların tedavisi

NORMAL

SEMPTOM ÖNCESİ

HAFİF KOGNİTİF BOZUKLUK

ALZHEİMER

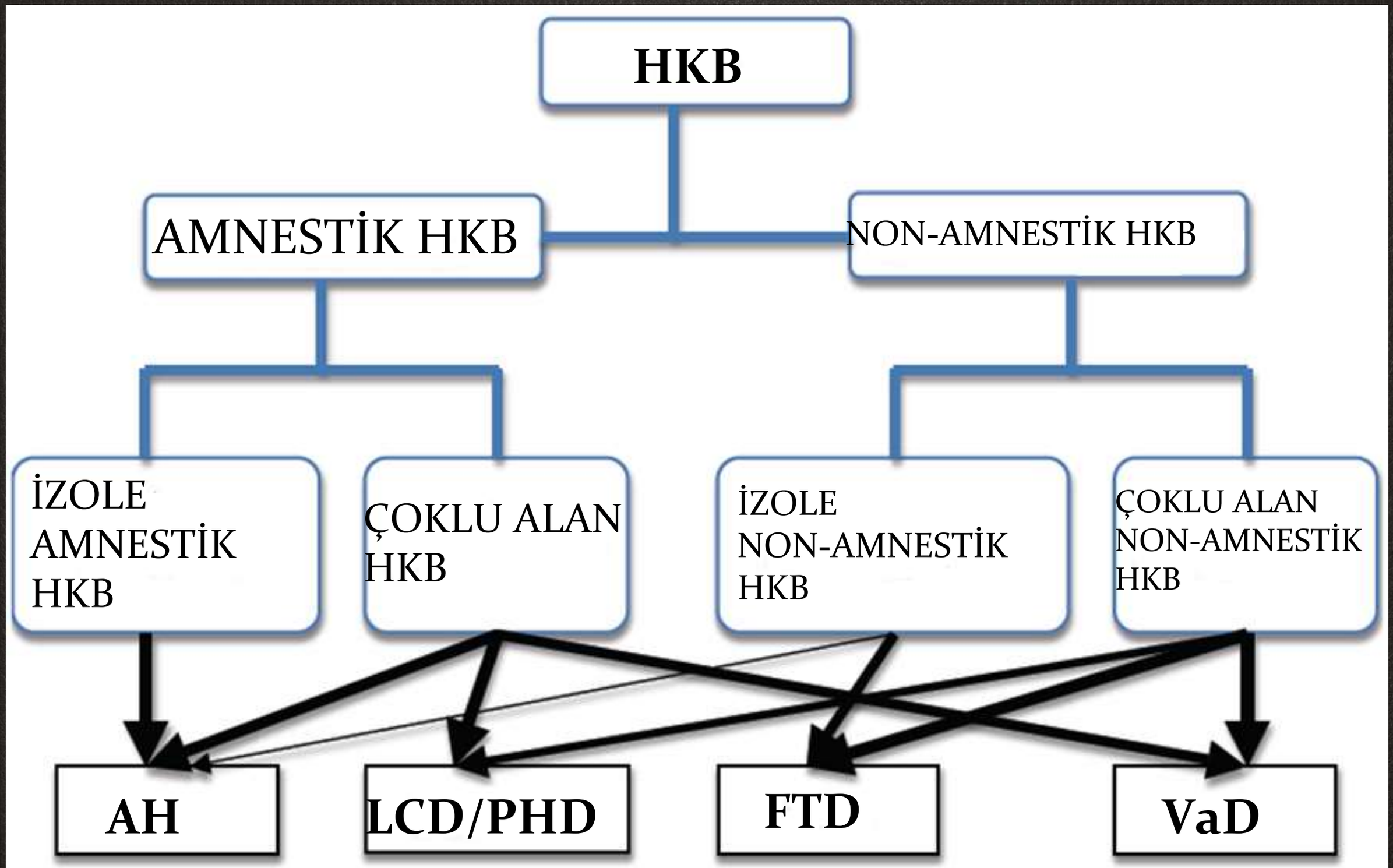
Semptom ve patoloji yok

Semptom yok erken patoloji

Alzheimer patolojisi ve bellek bozukluğu

ciddi patoloji
Orta ciddi kognitif bozukluk

ALZHEİMER HASTALIĞI


HKB
AMNESTİK HKB
NON-AMNESTİK HKB
İZOLE AMNESTİK HKB
ÇOKLU ALAN HKB
İZOLE NON-AMNESTİK HKB
ÇOKLU ALAN NON-AMNESTİK HKB
AH
LCD/PHD
FTD
VaD

Hastanın kognitif disfonksiyon şikayeti var mı? / Hasta yakını kognitif disfonksiyon bildiriyor mu?

HAYIR

EVET

Hastanın depresyon belirti /bulguları var mı?

Hastanın sistemik bir hastalığı var mı? Kronik ilaç kullanımı var mı?

EVET

Uygun tedavi sonrası yeniden değerlendir

EVET

Kronik hastalık ve ilaç yan etkileri açısından değerlendir

HAYIR

Hasta günlük yaşam aktivitelerini bağımsız sürdürüyor mu?

HAYIR

DEMANS

ÖYKÜNÜN SONUNDA

- Çekirdek kognitif bulgu nedir?
- Başlangıç ve seyir nasıldır?
- Çekirdek ve ikincil kognitif bozuklukların GYA'ları etkileme düzeyi nedir?
- Davranışsal ve ikincil alanların katılım zamanlamaları ve şiddetleri nelerdir?

Demans tanısında rutin laboratuvar

		Tipik Tablolar	Atipik Tablolar
Rutin Biyokimya	Hemogram Elektrolitler Kalsiyum Kan şekeri ALT/AST BUN/Kreatinin Tiroid testleri B12 vitamini Folik asid Homosistein	+	+
Diğer Biyokimya	Sifilis serolojisi HIV serolojisi Otoantikorlar Amonyak	-	+
BT/MRG	MR-DWI MR-GRE	±	+
Nöropsikoloji		±	+
SPECT/PET		-	+
MR-Spektroskopi		-	+
EEG		-	+

		Tipik Tablolar	Atipik Tablolar
LP	Hücre sayısı Sitoloji Protein düzeyi OKB Anti-nöronal antikorlar Kanalopati antikorları Protein 14-3-3 Total tau p-tau $A\beta_{42}$	-	+
Genetik	Mendelyen kalıtım genlerinin taranması *APOE* ve *PGRN* kodon 178 gibi yatkınlık polimorfizmleri	-	+
Biopsi	Beyin Ter bezi Kas	-	+

+ gerekli, - gereksiz, ± bazen

MİNİ MENTAL DURUM MUAYENESİ
(MMSE)

Ad - Soyad: **Prot :** **Tarih :**

PUAN ☐

ORYANTASYON

ZAMAN ☐ **MEKAN** ☐

☐	Yıl	:	☐	Ülke	:
☐	Ay	:	☐	Kent	:
☐	Tarih	:	☐	Hastane	:
☐	Gün	:	☐	Bölüm	:
☐	Mevsim	:	☐	Kat	:

KAYIT ☐

☐ Mavi ☐ Şahin ☐ Lale

DİKKAT ☐

100 _____☐ _____☐ _____☐ _____☐ _____☐

A ☐ Y ☐ N ☐ Ü ☐ D ☐

HATIRLAMA ☐

☐ Mavi ☐ Şahin ☐ Lale

DİL

ADLANDIRMA

Kalem ☐ Saat ☐

TEKRARLAMA

"O gelmiş olsaydı ben de giderdim." ☐

ANLAMA

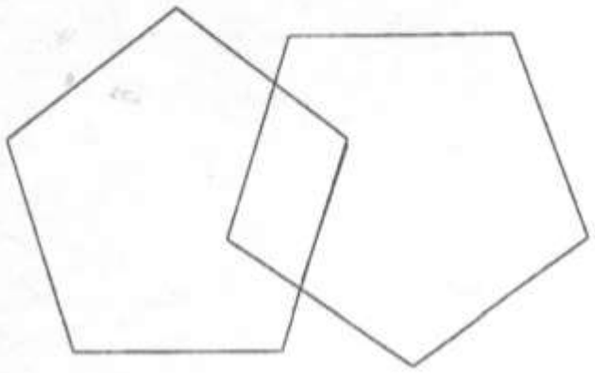
Kağıdı elinize alın, ☐ ortadan ikiye katlayın, ☐ ayağınızın dibine bırakın. ☐

YAZI ☐

OKUMA ☐

GÖZLERİNİZİ KAPAYIN

KOPYA ☐

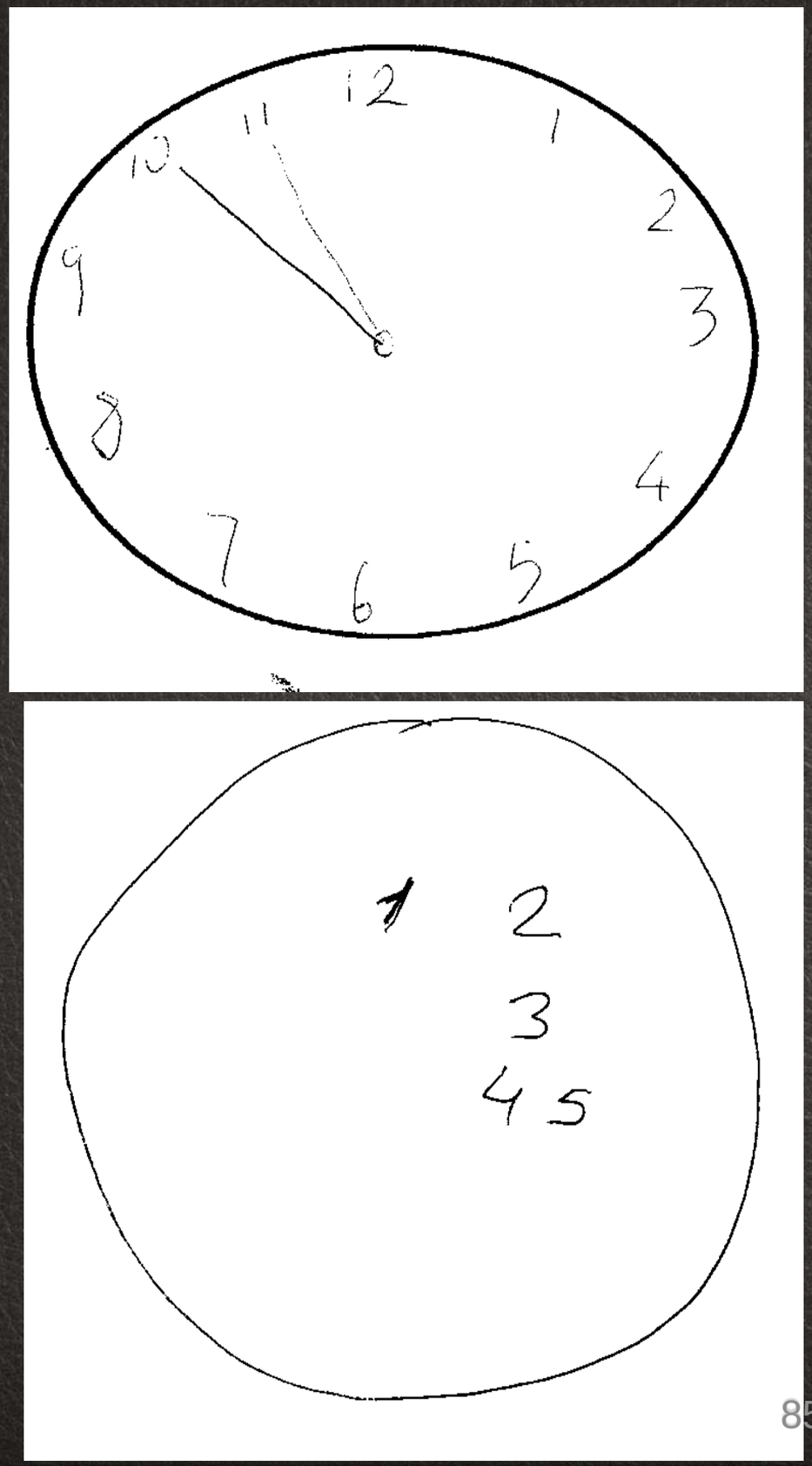


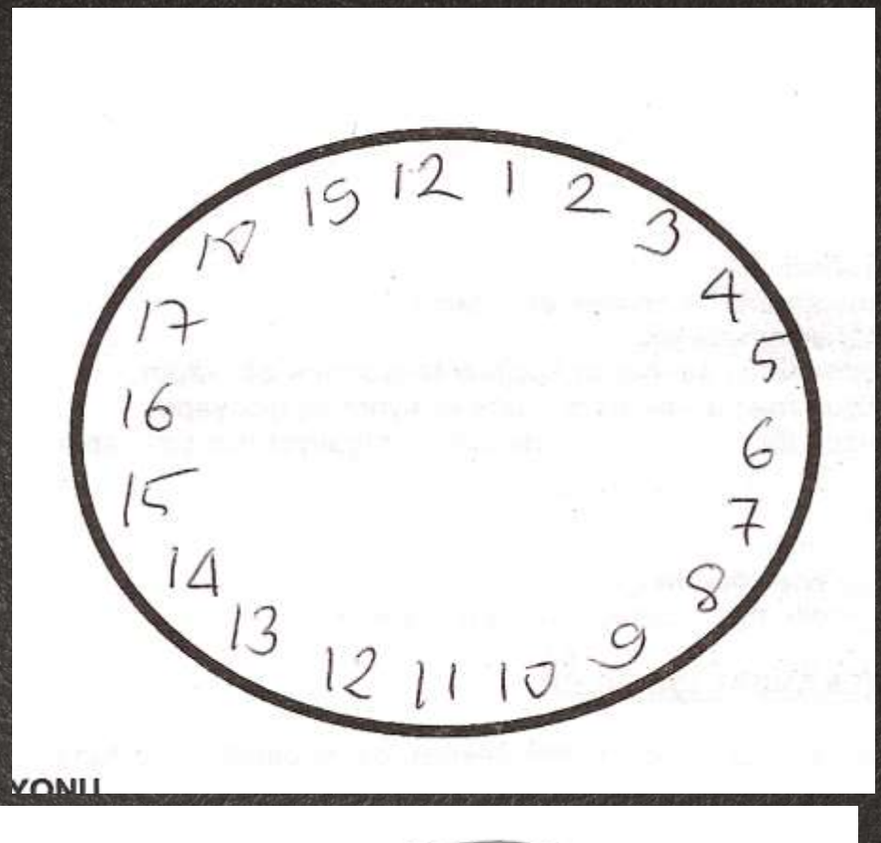
CDR			GDS
0	Normal yaşlanma **MMSE ≥ 25**	Bellekle ilgili yakınmalar yok veya özel isim unutma gibi sübjektif yakınmalar	1 2
0.5	MCI **MMSE ≥ 25**	İlerleyici unutkanlık, objektif yakın bellek bozukluğu, GYA'larda bozulma yok	3
1	Hafif demans **MMSE 20-24**	Çoğul kognitif bozukluklar, enstrümental GYA'larda bozulma: hobiler, mali işler, yabancı mekanda yön bulma, alet kullanma, ± depresyon	4
2	Orta demans **MMSE 10-19**	Kognitif bozulmada artış, ev çevresinde yön bulma, iletişim, temel GYA'larda güçlük: giyinme, yıkanma, beslenme; davranışsal problemler: hezeyan, hallusinasyon, anksiyete, fobiler	5
3	Ağır demans **MMSE 0-9**	Global kognitif yıkım, temel GYA'larda tümüyle bağımlı, ajitasyon, amaçsız tekrarlayıcı hareketler, sfinkter kontrol kusuru, yürüyüş bozukluğu	6 7

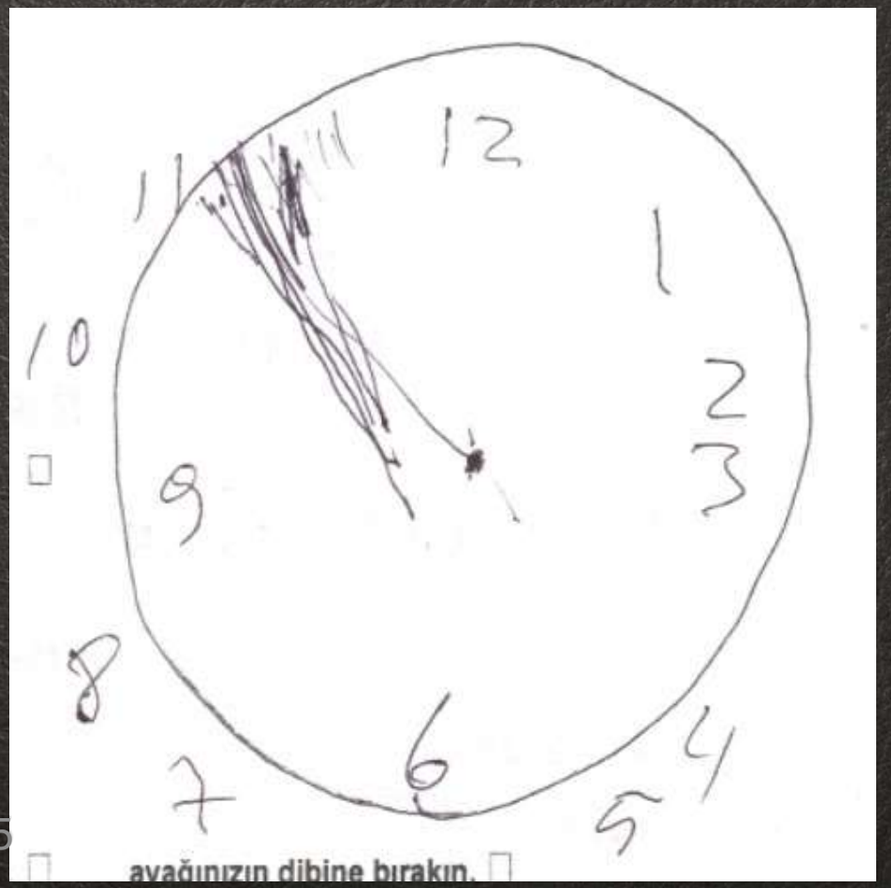
1 2 3 4 5 6 7 8 9 10 11 12 13

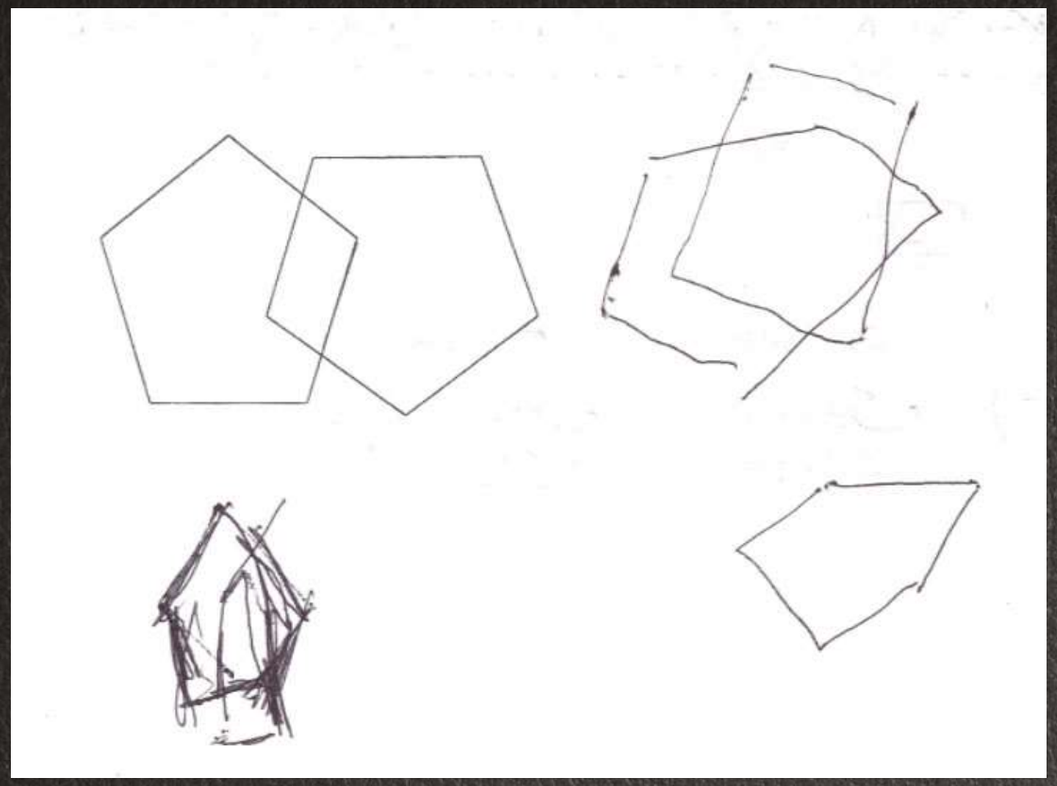
Yıl

APRAKSİ



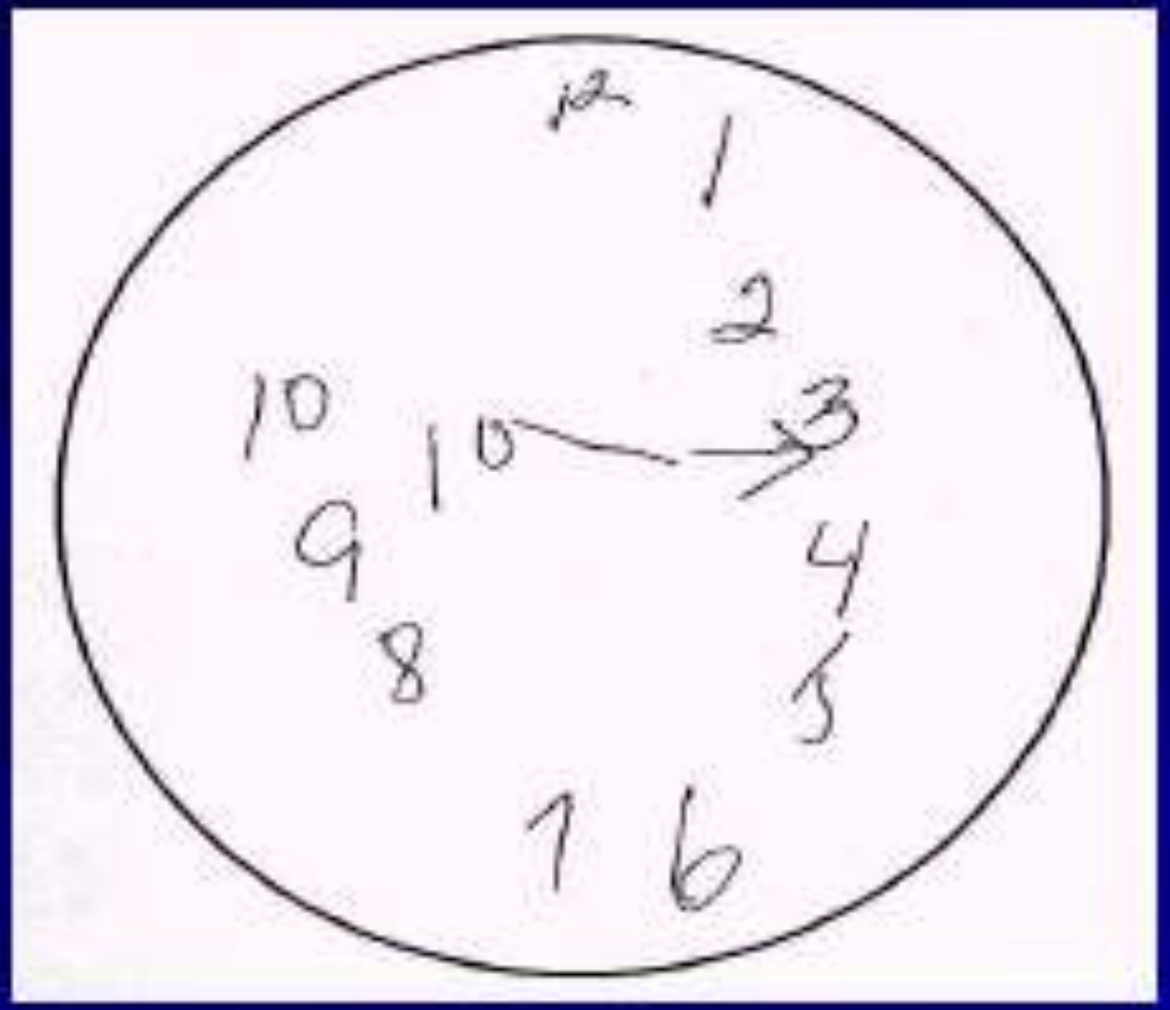


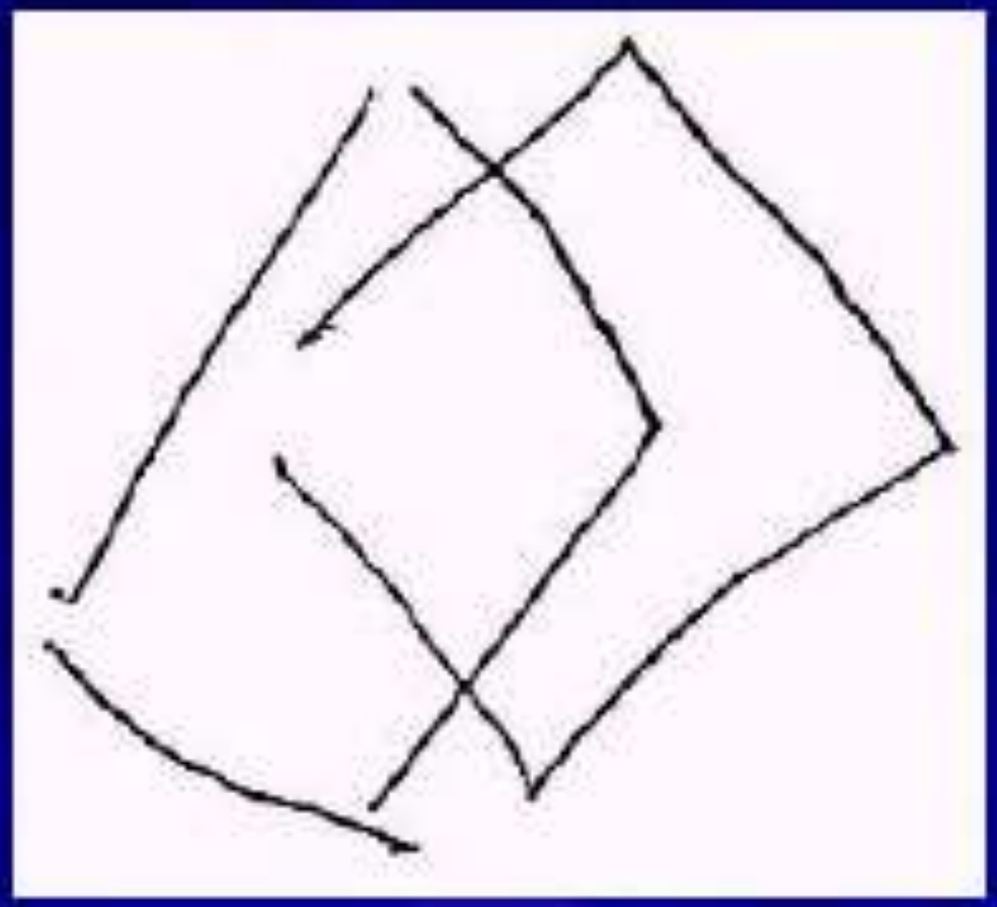

ayağınızın dibine bırakın.

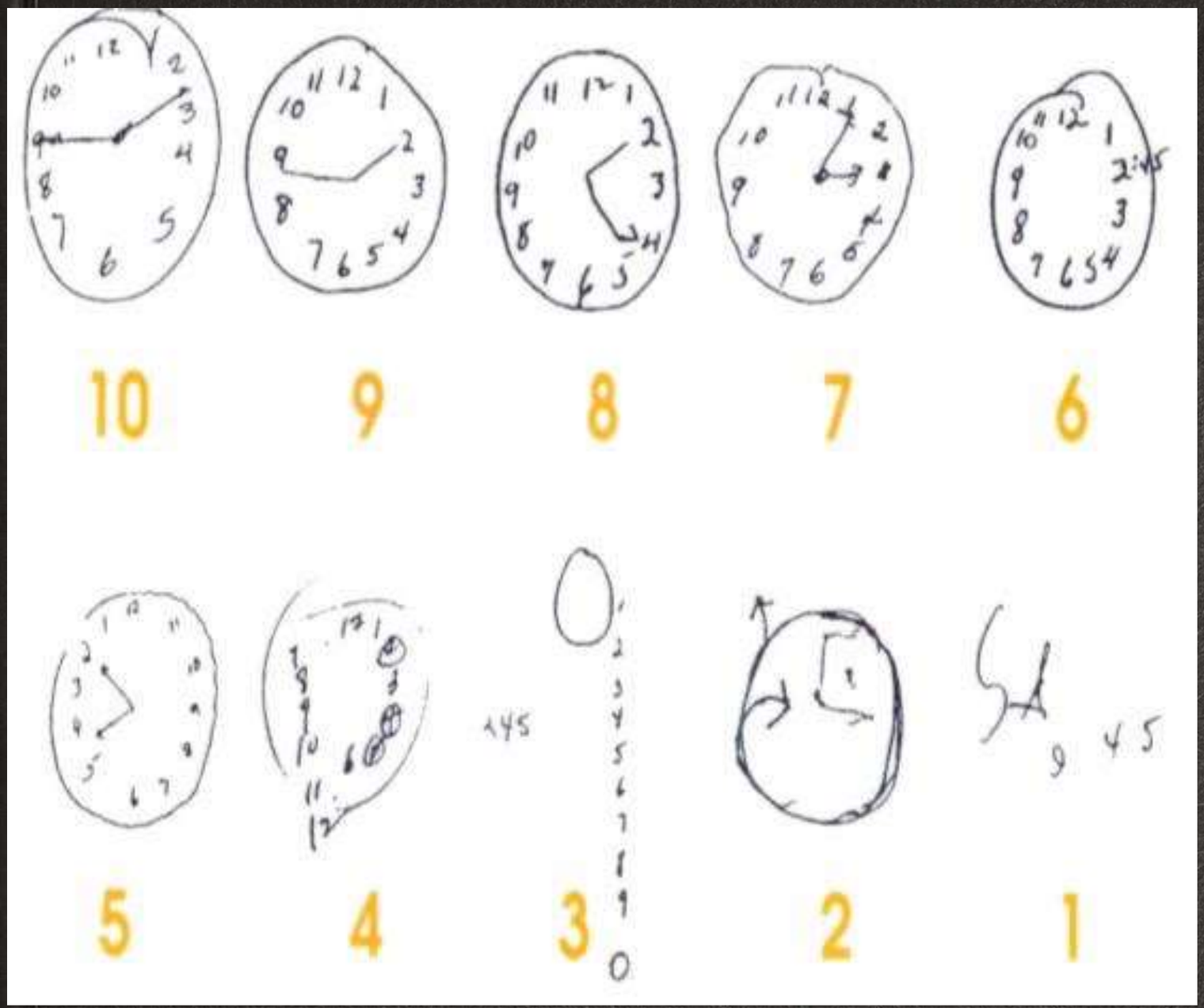


ayağınızın dibine bırakın.

Alzheimer Hastağında saat çizme ve kopyalama bozukluğu







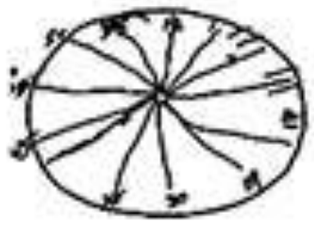
Anamnez, fizik muayene, mini mental test, saat çizme testi, geriatrik depresyon skalası ile takip etmeliyiz.

Saat Çizme Testi

Clock Drawings

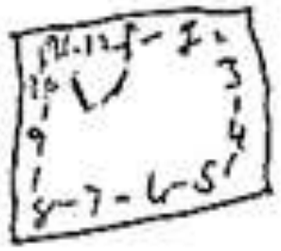
1) Score: _____

11-10

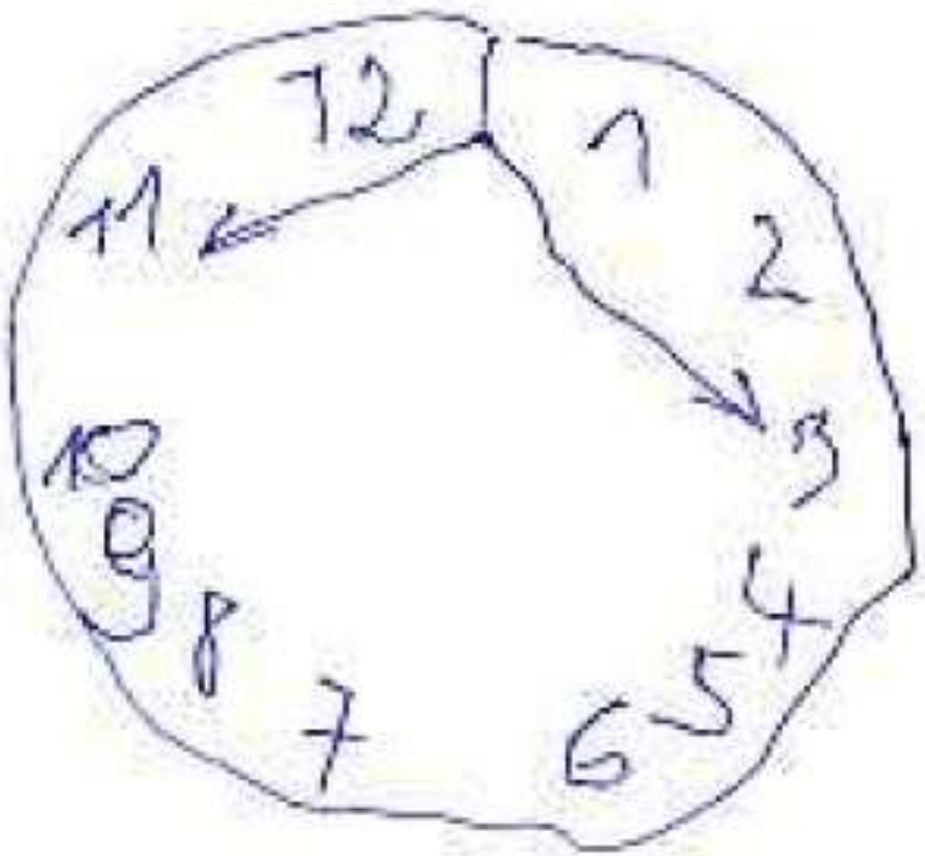


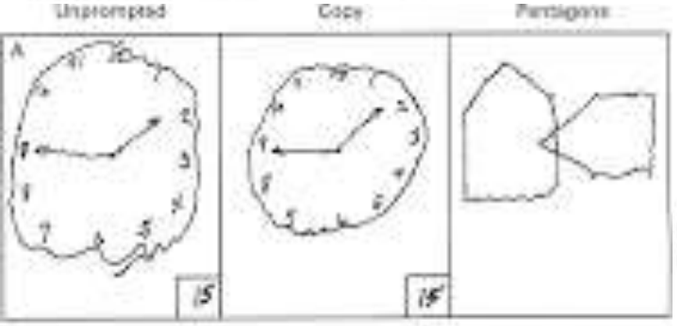
2) Score: _____

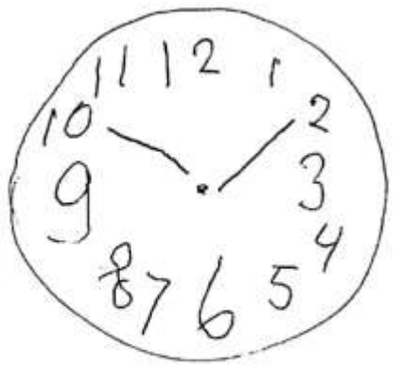
3) Score: _____

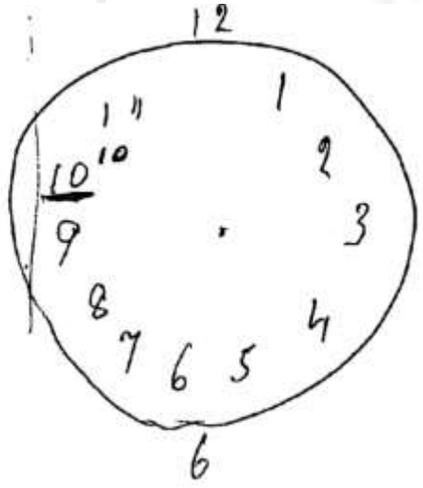


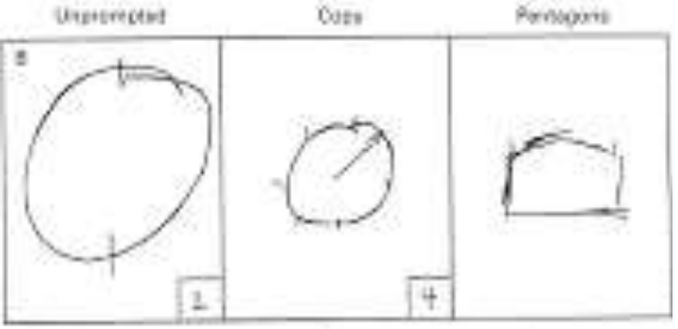
4) Score: _____

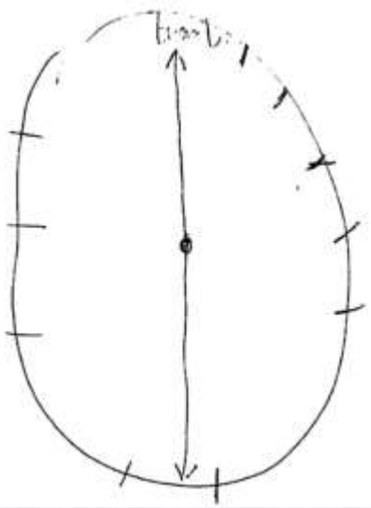


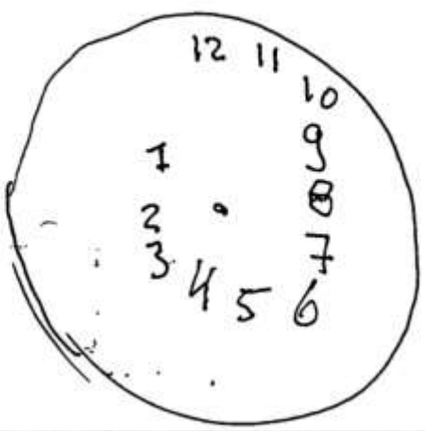


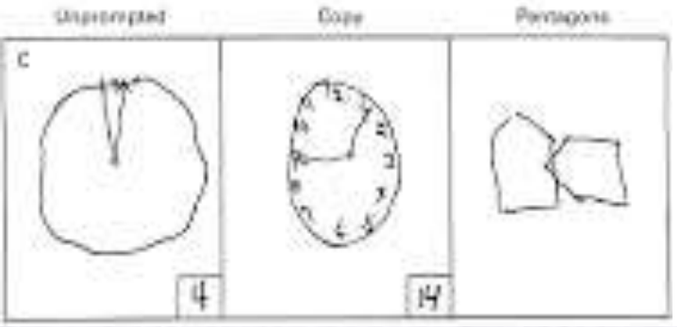


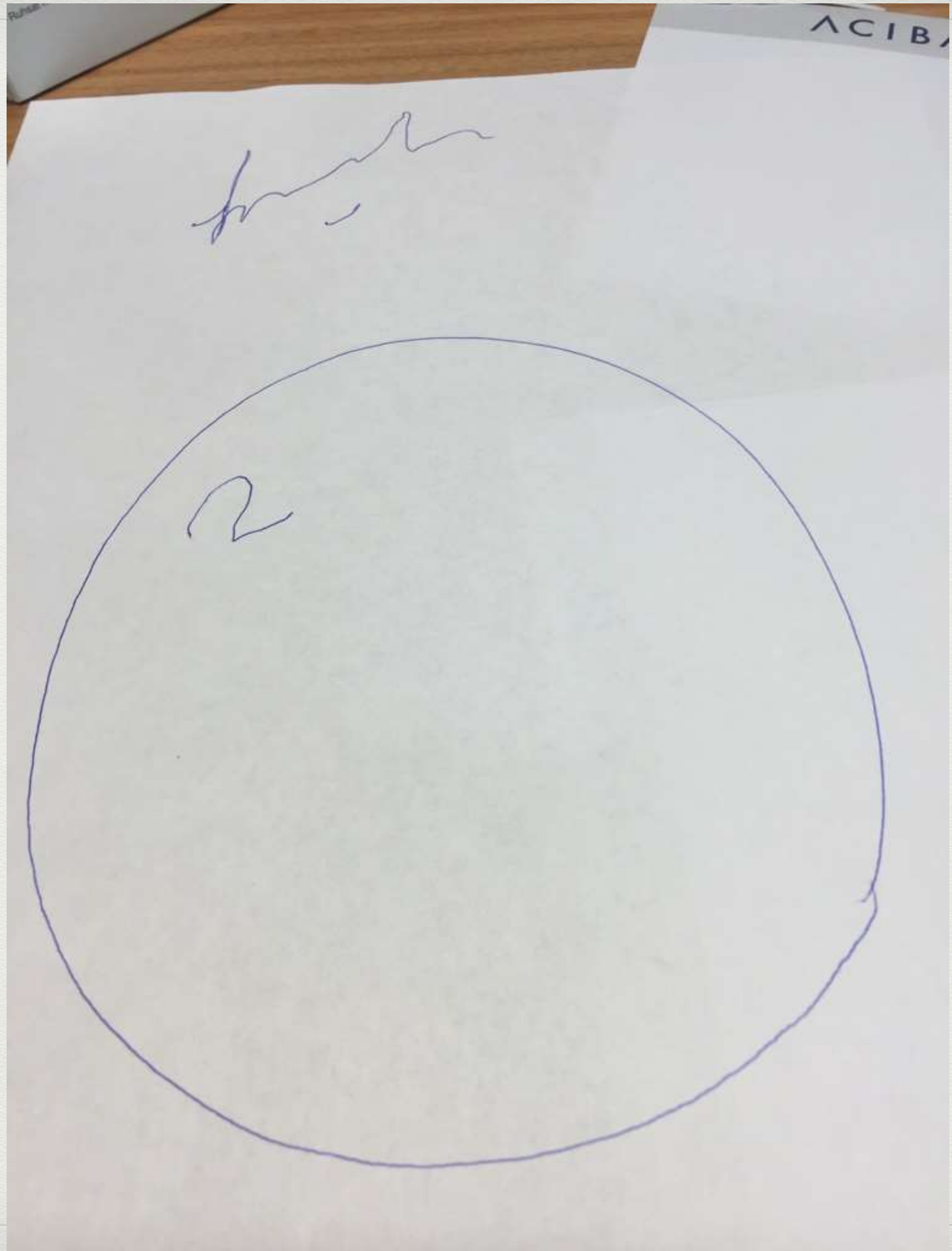


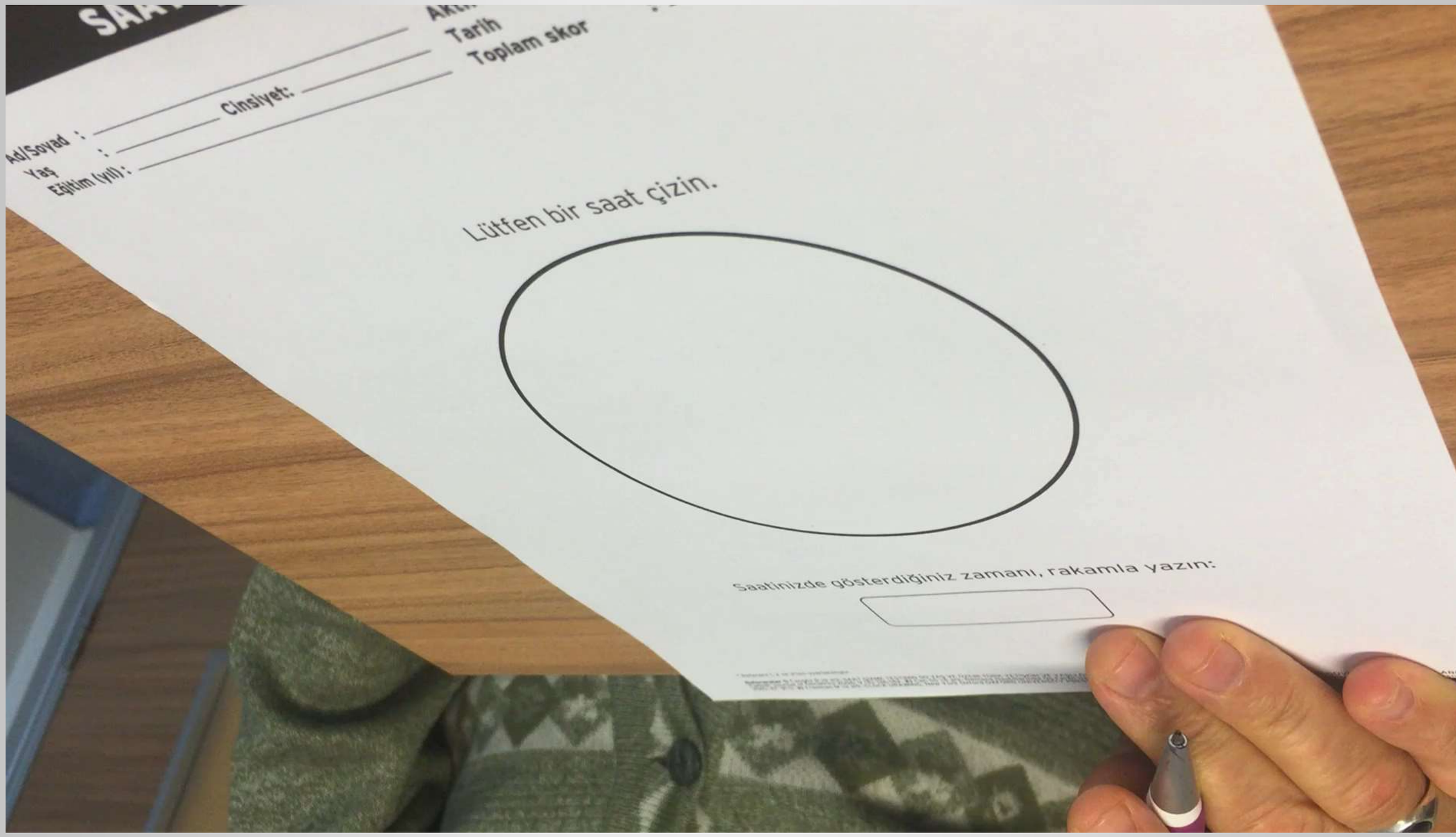




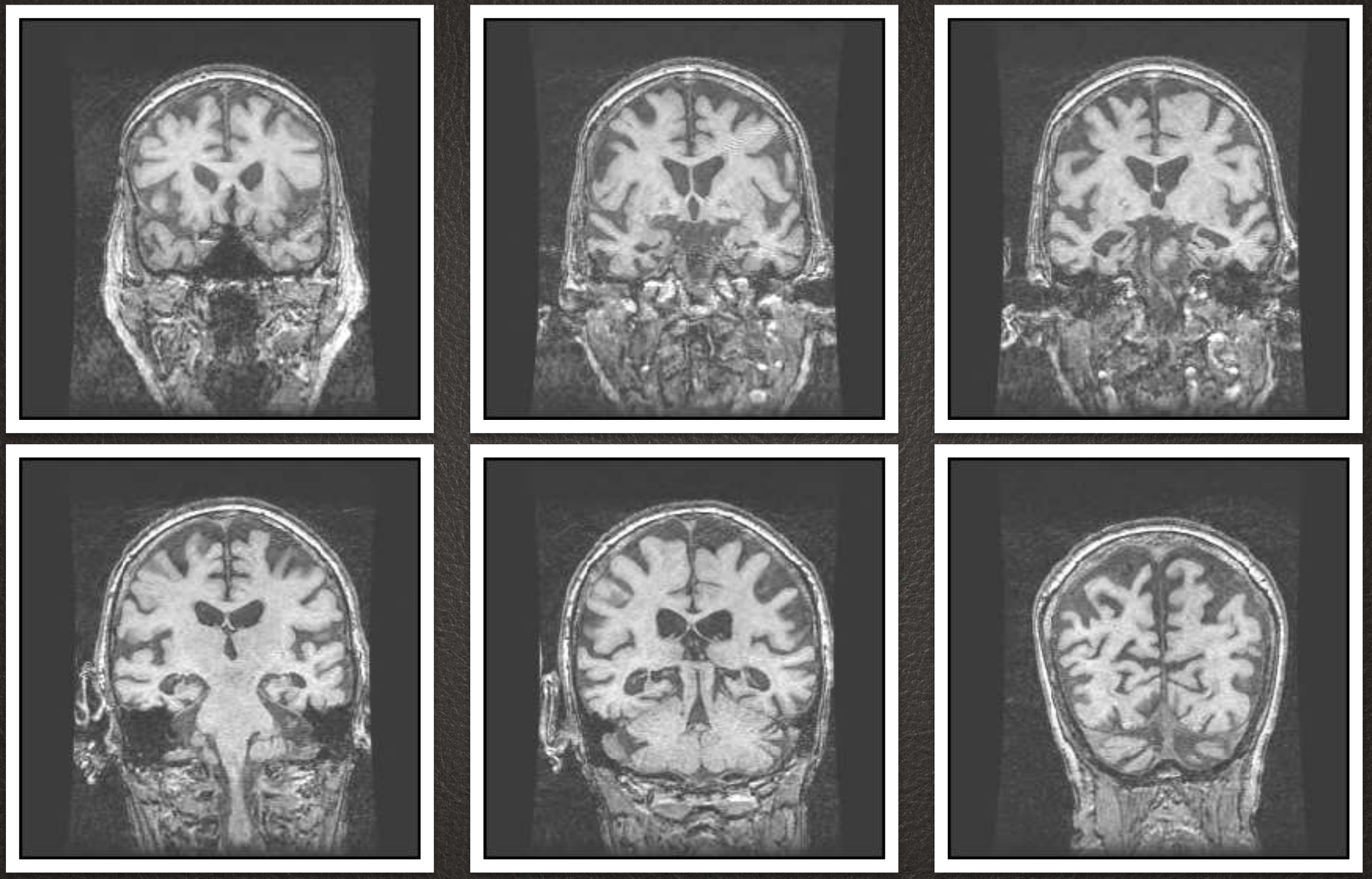







Ad/Soyad :
Yaş :
Eğitim (yıl):
Cinsiyet:
Tarih
Toplam skor
Lütfen bir saat çizin.
Saatinizde gösterdiğiniz zamanı, rakamla yazın:

Alzheimer Hastalığı-Ağır evre



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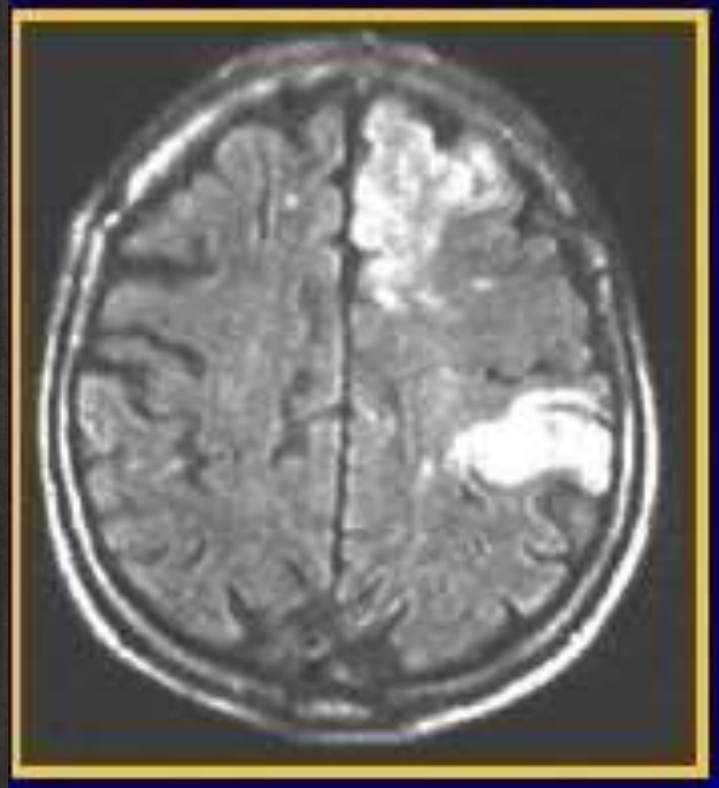
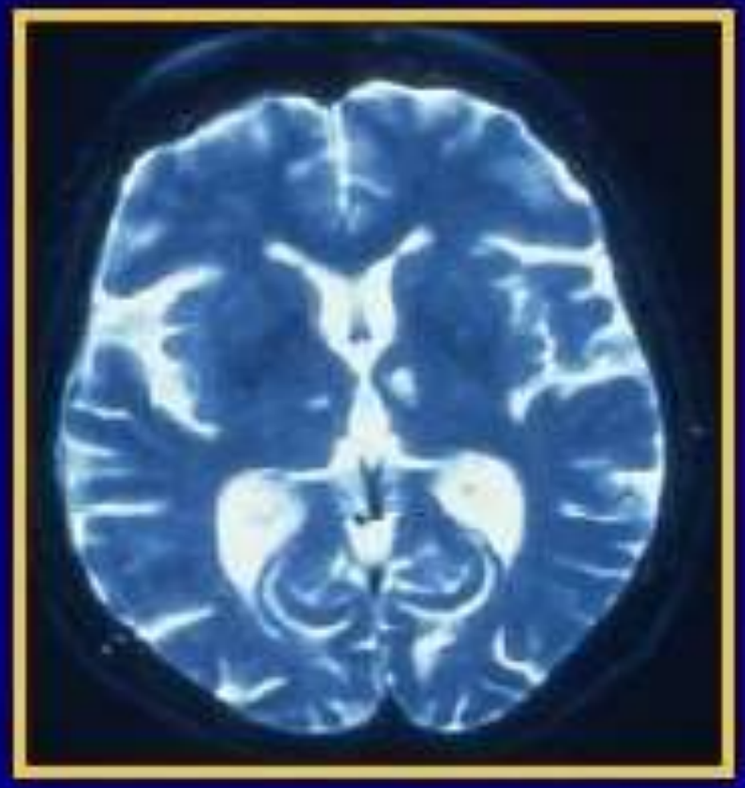
PRİMER(DEJENERATİF)	SEKONDER
Alzheimer hastalığı	Vasküler demans
Lewy cisimcikli demans	•Multi-infarkt demans
Fronto-temporal demans	•Binswanger hastalığı
FTD-davranışsal varyant	•Stratejik infarkt demansı
İlerleyici tutuk afazi	•CADASIL
Semantik demans	Normal basınçlı hidrosefali
FTD-ALS	Toksik-metabolik demanslar
Hareket bozukluğuyla birlikte	Wernicke-Korsakoff hastalığı
Parkinson hastalığı demansı	B12 vitamin eksikliği
Kortiko-bazal dejenerasyon	Hipotiroidi
Progresif supranükleer paralizi	Kronik karaciğer hastalığı
Huntington hastalığı	Organik çözücülere maruz kalma
Multi-sistem atrofiler	İlaçlar
Wilson hastalığı	İnfeksiyonlar
Nöroakantositoz	Herpes simpleks ensefaliti
Prion hastalıkları	Nörosifilis
Creutzfeldt-Jacob hastalığı	Kronik menenjitler
Gerstmann-Sträussler-Scheinker hastalığı	HIV-demans kompleksi
Fatal familyal insomni	Whipple hastalığı
Çeşitli pediyatrik demanslar	Kafa içi yer kaplayıcı hastalıklar
Kufs hastalığı	Neoplastik durumlar
Metakromatik lökodistrofi	Subdural hematom
Gaucher hastalığı	Otoimmun-inflamatuar hastalıklar
Niemann-Pick hastalığı	Multipl skleroz
Diğer ender demanslar	Behçet hastalığı
Limbik demans	Paraneoplastik limbik ensefalit
Poliglukozan cisimcik hastalığı	VGKC ve NMDAR kanalopatileri
Arjirofilik tahıl hastalığı	Granülomatöz anjitis
	Primer sinir sistemi vasküliti
	NAIM sendromu

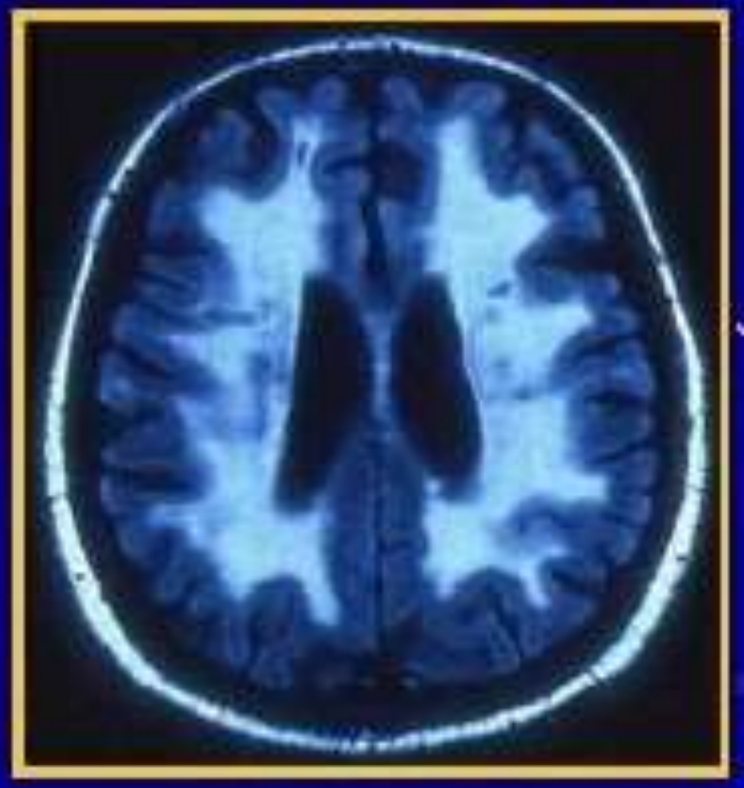
Multiple large vessel infarctions



Strategic infarctions



Subcortical VaD



FRONTOTEMPORAL DEMANS

Destekleyici bulgular

Davranışsal bozukluklar

- Kişisel hijyende bozulma
- Mental rijidite
- Çabuk çelinebilirlik
- Hiperoralite-diyette değişiklik
- Perseveratif ve stereotipik hareketler

<u>Destekleyici bulgular</u>

Konuşma-dil ile ilgili

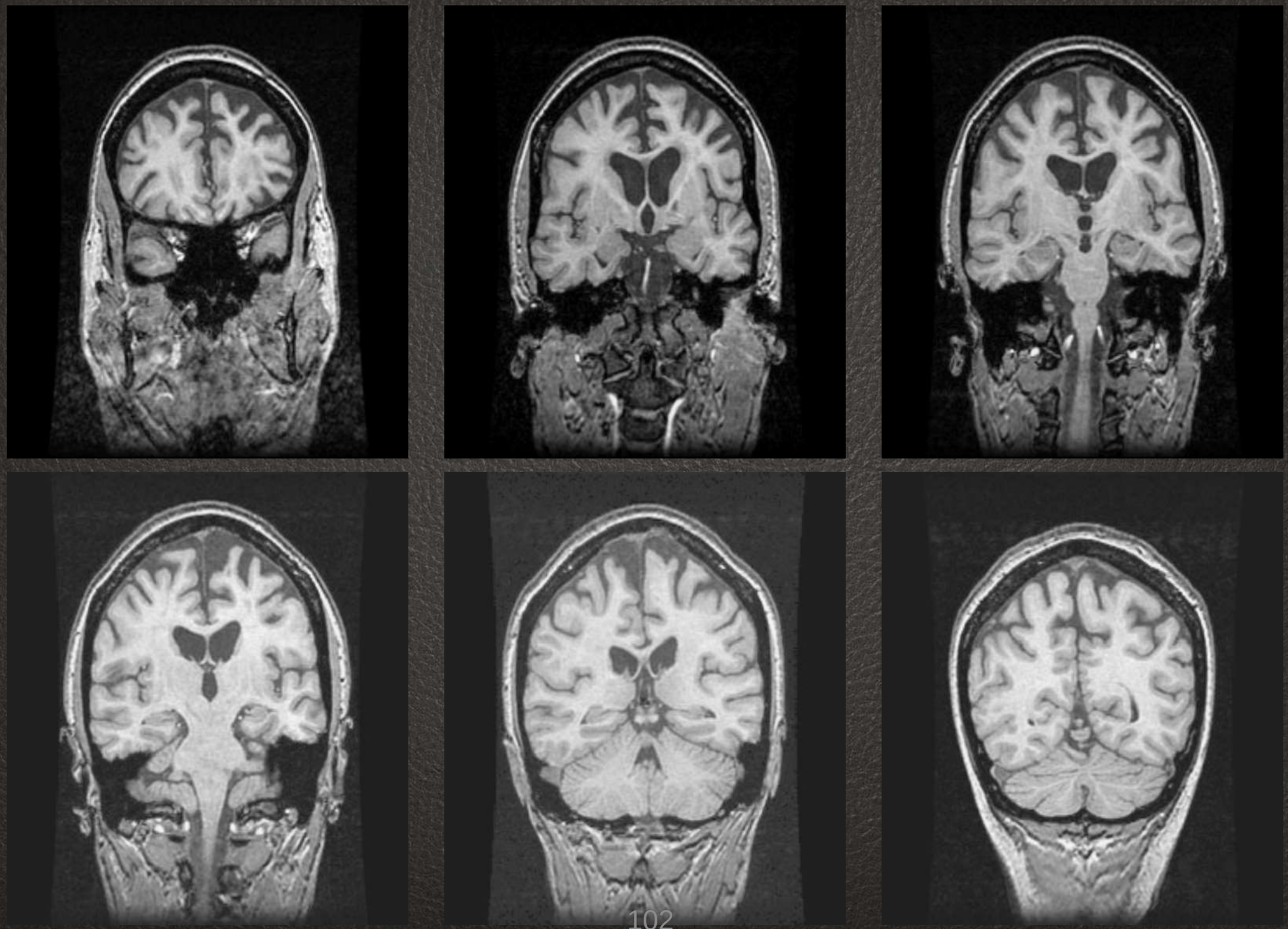
- Konuşma çıkışında değişiklik
- Kendiliğindenlik kaybı ve ekonomik konuşma
- Basınçlı konuşma
- Stereotipik konuşma
- Ekolali
- Perseverasyon
- Mutizm

Destekleyici bulgular

Fiziksel bulgular

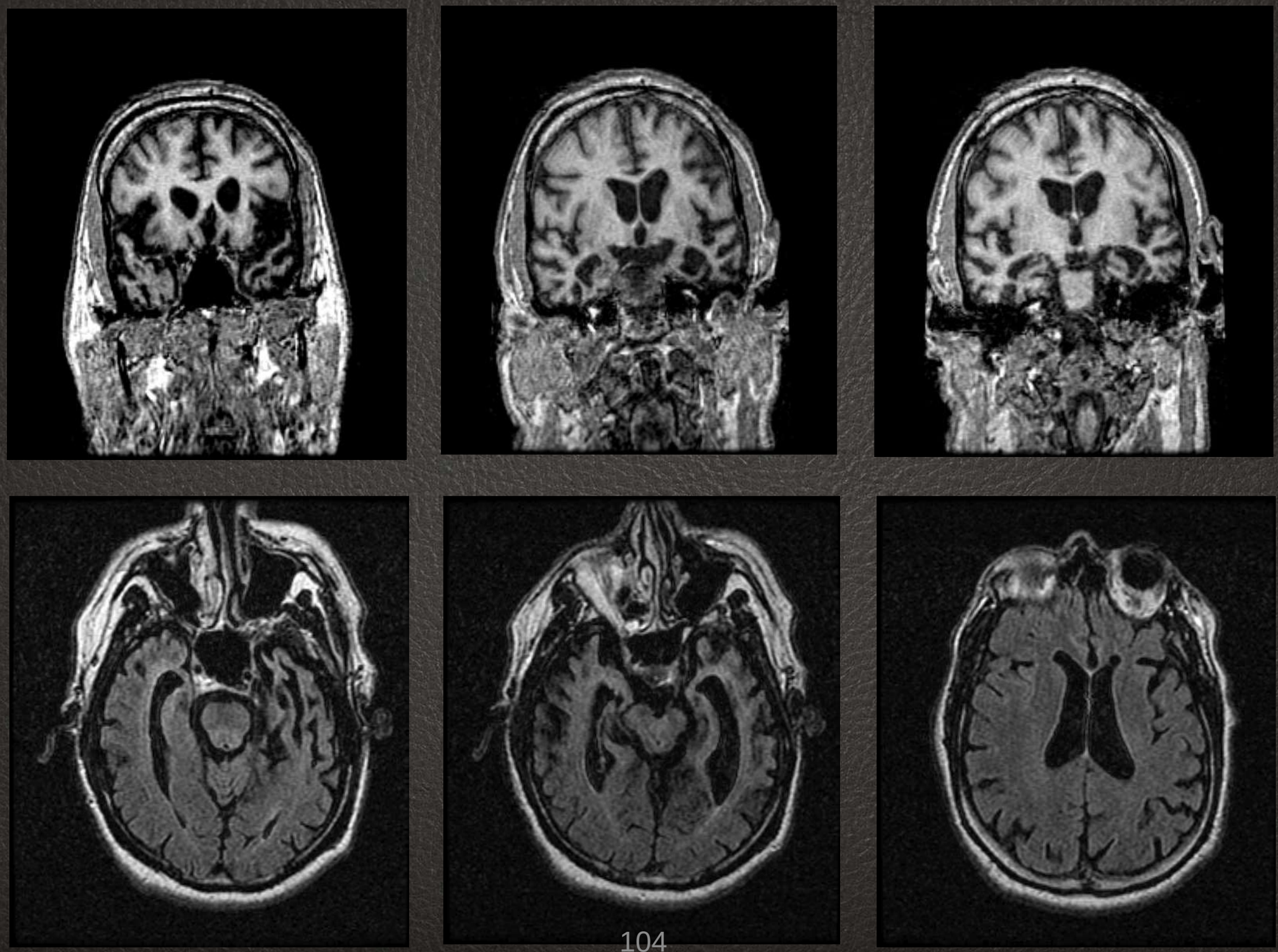
- Primitif refleksler
- İnkontinans
- Akinezi, rigidite, tremor
- Düşük ve labil kan basıncı

Frontotemporal Demans



Semantik Demans

MRG Bulgusu-ağır



Birinci basamak açısından önemli bir sorun mudur?

Demans Sendromun'um yaşla birlikte hem insidansı hem prevelansı artmaktadır. Tüm demans nedenleri için insidans yılda 75/100 000'dır. Alzheimer Hastalığı prevalansı 65 yaşında %10,3 iken, 65-85 yaşları arasında hastalık prevalansı her 5 yılda bir 2 kat artarak 80 yaşın üzerinde %47'ye ulaşmaktadır.

TANISI KONMAMIŞ DEMANS HASTALARI İLE EN ÇOK BİRİNCİ BASAMAK HEKİMLERİ KARŞILAŞMAKTADIR

MİNİ MENTAL DURUM MUAYENESİ
(MMSE)

Ad - Soyad: **Prot :** **Tarih :**

PUAN ☐

ORYANTASYON

ZAMAN ☐ **MEKAN** ☐

☐	Yıl	:	☐	Ülke	:
☐	Ay	:	☐	Kent	:
☐	Tarih	:	☐	Hastane	:
☐	Gün	:	☐	Bölüm	:
☐	Mevsim	:	☐	Kat	:

KAYIT ☐

☐ Mavi ☐ Şahin ☐ Lale

DİKKAT ☐

100 _____☐ _____☐ _____☐ _____☐ _____☐

A ☐ Y ☐ N ☐ Ü ☐ D ☐

HATIRLAMA ☐

☐ Mavi ☐ Şahin ☐ Lale

DİL ☐

ADLANDIRMA

Kalem ☐ Saat ☐

TEKRARLAMA

"O gelmiş olsaydı ben de giderdim." ☐

ANLAMA

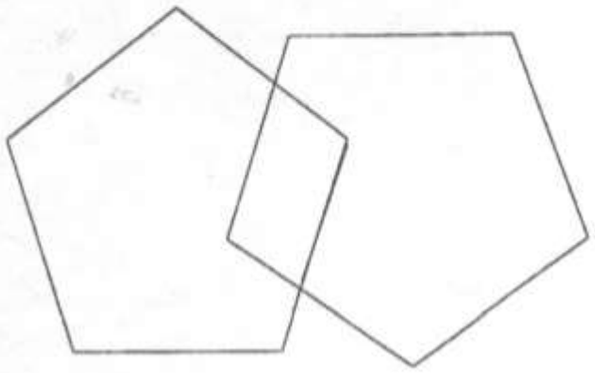
Kağıdı elinize alın, ☐ ortadan ikiye katlayın, ☐ ayağınızın dibine bırakın. ☐

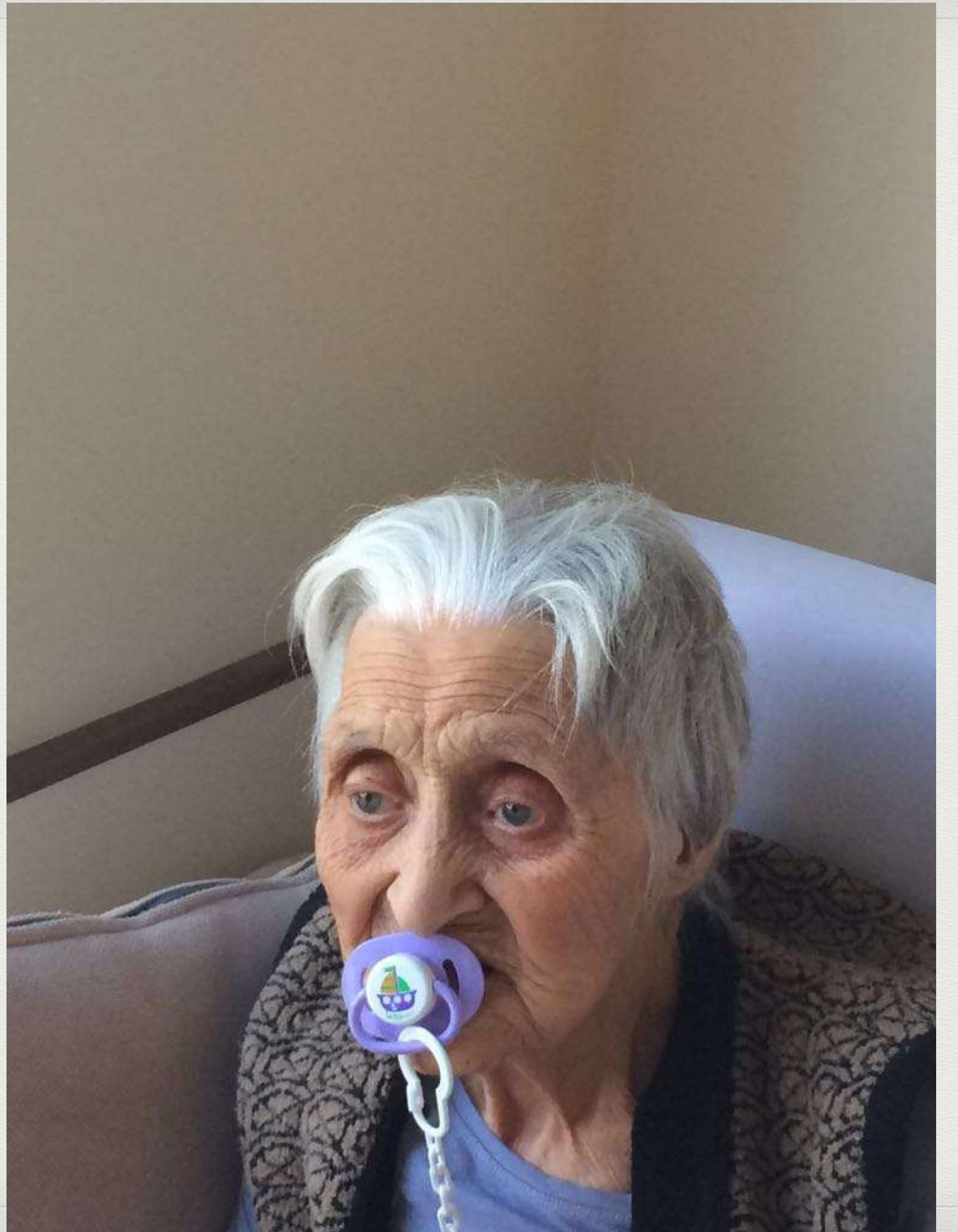
YAZI ☐

OKUMA ☐

GÖZLERİNİZİ KAPAYIN

KOPYA ☐





1967

1996

1997

1998

1999

2000