Kliiniline küsimus nr.5

Kas kõikidele dementsussündroomiga patsientidele teha haiguse diferentsiaaldiagnostikaks lisauuringuid, nt liikvori uuringud, elektroentsefalograafia, vs. mitte?

Tulemusnäitajad: ravitavate dementsuste diagnoosimine, teiste dementsussündroomi põhjustavate haiguste välistamine.

Kokkuvõte: Kõige põhjalikumalt käsitleb teemast ENFS, APA ja NICE ravijuhendid. Lisauuringute all mõeldakse liikvori uuringuid, elektroentsefalograafiat (EEG) ja geenitestimist.

Liikvori uuringud: ENFS juhendi alusel on soovitatud atüüpilistel juhtudel (hea praktika tava). Teha juhul, kui kahtlustatakse vaskuliiti, põletikulist, hematoloogilist, demüeliniseerivat haigust või Creutzwald-Jakobi tõbe (CJD) (B taseme soovitus). AT korral esinevad muutused liikvoris (Ab42 taseme langus, tau ja fosfo-tau valgu hulga tõus) toetavad diagnoosi (B taseme soovitus). APA ravijuhendi alusel ei ole piisavalt tõenduspõhisust, et kasutada rutiinses kliinilises praktikas. NICE ravijuhendi alusel tuleks teha kiiresti progresseeruva dementsuse korral. Canada ja NIAAA ravijuhendid ei soovita kasutada kliinilises praktikas.

EEG uuringut käsitlevad EFNS ja NICE ravijuhendid. EEG-st võib olla kasu atüüpilise AT korral. EEG võib anda infot varajase CJD, toksilis-metaboolse häire, võimaliku epileptilise amneesia või muu haiguse korral. EFNS ravijuhendis tuuakse EEG uuringu teostamine atüüpilise AT korral välja hea praktika tavana, CJD või epileptilise amneesia korral B taseme soovitusena. NICE ravijuhendi alusel ei tohiks EEG olla kasutusel rutiinse meetodina. Tuleks kaaluda, kui on kahtlus deliiriumile, frontotemporaalsele dementsusele või CJD-le. Ka patsientidel, kel kaasub dementsusega krambisündroom.

Geenitestimine: ApoE4 ei soovitata testida, kuna võib esineda ka normaalsetel eakatel. Varase algusega dementsed suunata spetsialiseeritud keskustesse, kus otsustatakse geenitestimise vajadus.

Soovitused:

1. Rutiinne liikvori uurimine Alzheimeri tõve diagnostikas ei ole soovitav (**tugev negatiivne soovitus**)
2. Elektroentsefalograafia ei ole rutiinses Alzheimeri tõve diagnostikas soovitav (**nõrk negatiivne soovitus**)
3. EEG-st võib olla kasu erijuhtudel: atüüpiline ja kiiresti progresseeruv dementsus, Creutzwald-Jakobi tõve kahtlus, deliirium, dementsusega kaasuv krambisündroom, jne (**töörühma praktiline soovitus**) – või kirjutada lahti tekstis?
4. Rutiinne ApoE4 genotüübi testimine ei ole soovitav (**tugev negatiivne soovitus**)
5. Perekondlike ja varase algusega dementsuse korral on soovitav haiged suunata spetsialiseeritud keskustesse - mälukliinikusse? Geneetiku vastuvõtule? (**töörühma praktiline soovitus**)

Süstemaatilised ülevaated

1.Ritchie C, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD008782

Cochrane süstemaatiline ülevaade, tasuta kättesaadav vaid abstract, mistõtti AMSTAR ei ole kohaldatav.

Uuriti liikvori ja plasma amüloid beeta määramist kerge kognitiivse dementsusega patsientidel, diagnoosimaks Alzheimeri tõbe. Metaanalüüsi kaasati 14 uuringut, neist 1349 inimest, kellel 436 arenes välja Alzheimeri tõbi. Uuringu sensitiivsus 36-100% (mediaan 81%), spetsiifilisus 29-91% (mediaan 64%). Uuringute vahel suur heterogeensus, kvaliteet varieerub ja jälgimisaeg ebapiisav. Ka sensitiivsus ja spetsiifilisus varieerub suurtes piirides.

Kokkuvõte: Liikvori beeta-amüloidi taseme langus omab väga väikest diagnostilist kasu ja marginaalset kliinilist väärtust. Kerge kognitiivse langusega patsientidel ei soovitata liikvori beeta-amüloidi määramist Alzheimeri tõve diagnoosimiseks.

2.Ruan, et al. Potential fluid biomarkers for pathological brain changes in Alzheimer's disease: Implication for the screening of cognitive frailty. MOLECULAR MEDICINE REPORTS 14: 3184-3198, 2016

AMSTAR: 9/11

Süstemaatiline ülevaade, mis uurib biomarkereid AT ja MCI diagnostikas. Uuritakse biomarkereid nii liikvoris, veres, kui ka uriinis. Liikvorist saab määrata tau-valgu, fosforüleerituf tau ja amüloid-beeta taset. Kehavedelike biomarkerid võivad olla kasulikud varases AT diagnostikas, ennustamaks prekliinilise dementsuse üleminekut AT-ks, eristamaks AT mitte-AT-st.

Liikvori Aβ42 aitab kõige paremini eristada AT frontotemporaalsest dementsusest.

3.Dawson Hedges, et al. P300 Amplitude in Alzheimer's Disease: A Meta-Analysis and Meta-Regression. Clinical EEG and Neuroscience 2016, Vol. 47(1) 48–55

AMSTAR: 9/11
AT korral esinevad muutused elektroentsefalograafial, mis võivad olla kasulikud diagnoosiks. Ülevaates uuritakse P300 komponendi muutusi. P300 komponent on kognitiivse aktiivsuse ja töömälu marker. Kognitsiooni languse korral esineb amplituudi langus. Langeb ka normaalse vananemise käigus. Tuuakse välja, et võib ollla tundlikum, kui neuropsühholoogiline testimine.

Uuringu kokkuvõttes tuuakse, et võrreldes tervete kontrollgrupiga, on AT haigetel P300 ampiltuud oluliselt madalam. Leiti ka seos haridustasemega, kuid amplituudi seost vanuse, patsiendi soo ja dementsuse raskusastmega ei leitud.

4.Aaron S. Howe. Meta-analysis of the endogenous N200 latency event-related potential subcomponent in patients with Alzheimer's disease and mild cognitive impairment. Clinical Neurophysiology 125 (2014) 1145–1151.

AMSTAR: 9/11
EEG uuringul on N200 amplituudi pikenemine seotud AT-ga, eristab normaalsest vananemisest. Ei ole aga erinevust kerge kognitiivse defitsiidiga patsientidega ja AT haigetega. Võib kasutada ka kognitsiooni languse jälgimisel.

5.Christina Micanovic, et al. The diagnostic utility of EEG in early-onset dementia: a systematic review of the literature with narrative analysis. J Neural Transm (2014) 121:59–69

AMSTAR: 10/11
EEG ei aita eristada dementsuse alatüüpi varajases staadiumis. Küll aga võib üldine fooni aeglustumine olla seotud alloleva neurodegeneratiivse põhjusega. EEG muutused on kõige väljendunumad AT ja Lewy keha dementsuse korral. Seetõttu võib EEG kasutada diagnoosi kinnitada, diferentsida teistest dementsusest (nagu frontotemporaalne dementsus).
AT korral esineb aeglase-laine aktiivsuse tõus (delta/teeta). Varasem algusega AT haigetel on nii fokaalseid kui difuusseid muutusi EEG-l võrreldes tervetega. Noortel AT haigetel on raskemad muutused EEGs ja madalamad MMSE skoorid võrreldes vanemate AT haigetega. 3 uuringut leidsid EEG muutuste seose dementsuse raskusastmega, aga mitte haiguse kestusega.

6.Vesna Jelic, et al. Evidence-Based EvaIuation of Diagnostic Accuracy of Resting EEG in Dementia and Mild Cognitive Impairment. CLINICAL EEG and NEUROSCIENCE. 2009VOL 40N0 2.

AMSTAR: 10/11
EEG kasutamine dementsuse ja MCI kliinilises diagnoosis ei oma piisavalt tõenduspõhiseid andmeid, et kasutada EEG esmases hindamises. Ei ole ühte kindlat neurofüsioloogilist markerit, esineb alfa lainete langus, teeta lainete tõus, üldise fooni langus AT haigetel.

7.Hanneke de Waal, et al. EEG abnormalities in early and late onset Alzheimer's disease: understanding heterogeneity. J Neurol Neurosurg Psychiatry 2011;82:67e71

Case control study
Võrreldi EEG muutusi varase ja hilise algusega (>65 ja <65.a.) AT haigetel ja selle korrellatsiooni APOE4 genotüübiga. Tulemustest selgus, et noorematel AT haigetel olid EEG muutused enam väljendunud, kui vanematel. Samas, kui vanematel kontrollgrupi inimestel oli enam EEG muutusi kui noorematel. APOE4 negatiivsed patsiendid – raskemad EEG muutused.
KOkkuvõte: Varase algusega AT haiged, APOE4 genotüüp negatiivsed – EEG muutused enam väljendunud.

8. Olsson, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016; 15: 673–84

AMSTAR: 11/11
Hiljuti Lancetis avaldatud üstemaatiline ülevaade, kus hinnatakse liikvori biomarkereid. Kokku on vaadeldud 15 liikvori ja vere biomarkereid. Otsiti Pubmedist (4521 artiklit(ja Web of Science (231 artiklit), kokku 15699 patsienti. Liikvori T-tau, P-tau ja AB42 eristasid AT kontrollidest hästi (statistiliselt oluline). Liikvori NFL (neurofilament light protein) ja plasma T-tau olid hea tundlikkusega. Samas kui liikvori NSE, VLP-1, HFABP ja YKL-40 olid mõõduka tundlikkusega (uued biomarkerid).
Kliinilises praktikas kasutada T-tau, P-tau, AB42 ja NFL.

9. Jin-A Mo, et al. Cerebrospinal Fluid β-Amyloid1–42 Levels in the Differential Diagnosis of Alzheimer's Disease—Systematic Review and Meta-Analysis. PLOS ONE | DOI:10.1371/journal.pone.0116802 February 24, 2015

AMSTAR: 11/11
Metaanalüüsis uuritakse, kas liikvori beeta-amüloidi määramine aitab eristada AT teistest dementsustest. AT korral esineb liikvoris beeta amüloid 42 valgu langus. Aga beeta-amüloidi tase on fluktueeruv ajas ja individuaalselt. Ei ole paika pandud absoluutset piiri, mis diferentseeriksAT tervetest ja teistest dementsustest. Meta-analüüsi kaasati 10 uuringut (kokku 2211 AT haiget ja 1030 kontrolli).

Tulemused: Kuigi AT haigetel on amüloid-beeta tase keskmiselt kuni 50% madalam, kui tervetel kontrollides, et leitud cut-off piiri, mis aitaks kindlalt diferentsida. Ei diferentsi kontrolle ja MCI haigeid. Beeta amüloidi määramine aitab eristada AT ja mitte-AT haigeid. Aga beeta-amlüoid üksi ei ole piisav, et diagnoosida AT.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
1.Andmebaasid: MEDLINE (OvidSP), EMBASE (OvidSP), BIOSIS Previews (ISI Web of Knowledge), Web of Science and Conference Proceedings (ISI Web of Knowledge), PsycINFO (OvidSP), and LILACS (BIREME). The confidence in diagnosing mild cognitive impairment (MCI) due to Alzheimer's disease dementia is raised with the application of biomarkers based on measures in the cerebrospinal fluid (CSF) or imaging. These tests, added to core clinical criteria, might increase the sensitivity or specificity of a testing strategy. However, the accuracy of biomarkers in the diagnosis of Alzheimer's disease dementia and other dementias has not yet been systematically evaluated. A formal systematic evaluation of sensitivity, specificity, and other properties of plasma and CSF amyloid beta (Aß) biomarkers was performed. The proposed diagnostic criteria for prodromal dementia and MCI due to Alzheimer's disease, although still being debated, would be fulfilled where there is both core clinical and cognitive criteria and a single biomarker abnormality. From our review, the measure of abnormally low CSF Aß levels has very little diagnostic benefit with likelihood ratios suggesting only marginal clinical utility. The quality of reports was also poor, and thresholds and length of follow-up were inconsistent. We conclude that when applied to a population of patients with MCI, CSF Aß levels cannot be recommended as an accurate test for Alzheimer's disease.	1.Ritchie C, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD008782
2.Andmebaasid: MEDLINE, Pubmed. The present study focused on studies that assessed these biomarkers in AD, mild cognitive impairment and non-AD demented subjects. At present, widely used fluid biomarkers include cerebrospinal fluid (CSF), total tau, phosphorylated tau and amyloid-β levels. With the development of novel measurement techniques and improvements in understanding regarding the mechanisms underlying aging-related major neurocognitive disorders, numerous novel biomarkers associated with various aspects of AD neuropathology are being explored. These include specific measurements of Aβ oligomer or monomer forms, tau proteins in the peripheral plasma and CSF, and novel markers of synaptic dysfunction, neuronal damage and apoptosis, neuronal activity alteration, neuroinflammation, blood brain barrier dysfunction, oxidative stress, metabolites, mitochondrial function and aberrant lipid metabolism. The proposed panels of fluid biomarkers may be useful in the early diagnosis of AD, prediction of the progression of AD from preclinical stages to the dementia stage, and the differentiation of AD from non-AD dementia. In combination with physical frailty, the present study surmised that these biomarkers may also be used as biomarkers for cognitive frailty (CF), thus contribute to discovering causes and informing interventions for cognitive impairment in individuals with CF.	2.Ruan, et al. Potential fluid biomarkers for pathological brain changes in Alzheimer's disease: Implication for the screening of cognitive frailty. MOLECULAR MEDICINE REPORTS 14: 3184-3198, 2016

3. Andmebaasid: Medline, Web of Knowledge, and PsychINFO. Numerous biomarkers have been developed that can help in making an early diagnosis. The P300 is an event-related potential that may be abnormal in Alzheimer's disease. Given the possible association between P300 amplitude and Alzheimer's disease and the need for biomarkers in early Alzheimer's disease, the main purpose of this meta-analysis and meta-regression was to characterize P300 amplitude in probable Alzheimer's disease compared to healthy controls. Using online search engines, we identified peer-reviewed articles containing amplitude measures for the P300 in response to a visual or auditory oddball stimulus in subjects with Alzheimer's disease and in a healthy control group and pooled effect sizes for differences in P300 amplitude between Alzheimer's disease and control groups to obtain summary effect sizes. We also used meta-regression to determine whether age, sex, educational attainment, or dementia severity affected the association between P300 amplitude and Alzheimer's disease. Twenty articles containing a total of 646 subjects met inclusion and exclusion criteria. The overall effect size from all electrode locations was 1.079 (95% confidence interval = 0.745-1.412, P < .001). The pooled effect sizes for the Cz, Fz, and Pz locations were 1.226 (P < .001), 0.724 (P = .0007), and 1.430 (P < .001), respectively. Meta-regression showed an association between amplitude and educational attainment, but no association between amplitude and age, sex, and dementia severity. In conclusion, P300 amplitude is smaller in subjects with Alzheimer's disease than in healthy controls.	3.Dawson Hedges, et al. P300 Amplitude in Alzheimer's Disease: A Meta-Analysis and Meta-Regression. Clinical EEG and Neuroscience 2016, Vol. 47(1) 48–55
4. Andmebaasid: PsycINFO, PubMed, Medline, and Scopus Objectives: The N200 latency subcomponent has the potential to be an accurate neurophysiological marker of the cognitive deterioration seen in Alzheimer's disease (AD) and mild cognitive impairment (MCI). Methods: Standard mean difference (SMD) estimates of the N200 latency subcomponent were compared in three treatment groups: patients with AD, patients with MCI, and an unrelated elderly control group. Results: Patients with AD had significantly prolonged N200 latencies compared to the control group, pooled SMD: 0.866 (95% CI: 0.517 to 1.214, z = 4.87, p < 0.001). Patients with MCI had significantly prolonged N200 latencies compared to the control group, pooled SMD: 0.578 (95% CI: 0.213 to 0.943, z = 3.31, p = 0.002). When comparing patients with AD and MCI the N200 latencies were similar, pooled SMD: 0.096 (95% CI: 0.261 to 0.453, z = 0.53, p = 0.598). Conclusion: The abnormalities present in the N200 latency subcomponent validate previous research that N200 latency is an informative indicator of information-processing deterioration in patients with cognitive impairment. Significance: Clinically, measurements of N200 latency can be used as a risk assessment of elderly patients that	4.Aaron S. Howe. Meta-analysis of the endogenous N200 latency event-related potential subcomponent in patients with Alzheimer's disease and mild cognitive impairment. Clinical Neurophysiology 125 (2014) 1145–1151

may be progressing to mild cognitive impairment and/or Alzheimer's disease.	
5.Early-onset dementia (EOD) is characterized by functionally impairing deterioration in memory, language, personality or visuospatial skills emerging under the age of 65. Cerebral functioning can be assessed by visual electroencephalography (EEG) interpretation. The aim of this systematic review is to evaluate the diagnostic utility of visual EEG in EOD focusing on Alzheimer's disease (AD), vascular dementia (VAD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). Medline, Embase, Scopus, Web of Knowledge, and Google Scholar were systematically searched for studies where EEGs were included in the diagnostic evaluation of patients with dementia under the age of 65. Each paper was quality assessed and the results grouped according to dementia cause with a narrative summary. 4,157 papers were screened, 12 studies met the eligibility criteria with a total of 965 patients. An abnormal EEG was common to all causes of EOD. EEG abnormalities are more severe in early-onset AD patients. EEG severity grade is independent of disease duration. Slow wave activity is common to all dementias, but is most prominent in DLB. Frontal intermittent rhythmic delta activity could be considered as supportive for the diagnosis of DLB as can a Grand Total EEG score of over 9.5. EEG is usually normal in FTD. Focal changes can be seen in advanced VAD. Studies employed small patient groups, varying diagnostic criteria, and only a minority of patient diagnoses was pathologically confirmed. EEG may be useful as an adjunct in the diagnosis of DLB and AD. Further prospective well-powered studies are required to investigate diagnostic utility more robustly.	5.Christina Micanovic, et al. The diagnostic utility of EEG in early-onset dementia: a systematic review of the literature with narrative analysis. J Neural Transm (2014) 121:59–69
6.Using an evidence-based technique we searched for articles on diagnostic accuracy of spontaneous EEG in dementia disorders published from 1980 until June 2008. Inclusion criteria were: original article published in English with 10 or more subjects per diagnostic group, diagnosed according to the established consensus clinical diagnostic criteria used as a "gold standard." In addition, it should have been possible to calculate from the reported results indexes of diagnostic test accuracy: sensitivity, specificity, likelihood ratios and diagnostic odds ratios. Forty-six articles were retrieved that satisfied eligibility criteria. In conclusion, despite the wealth of published research and reported high indexes of diagnostic accuracy of EEG, and qEEG in particular, in individual studies, evidence of diagnostic utility of resting EEG in dementia and mild cognitive impairment (MCI) is still not sufficient to establish this method for the initial evaluation of subjects with cognitive impairment in the routine clinical practice. Joint effort of preferably multicenter studies using uniform standards should develop optimized methods, investigate added diagnostic value of EEG in clinically established dementia	6.Vesna Jelic, et al. Evidence-Based EvaIuation of Diagnostic Accuracy of Resting EEG in Dementia and Mild Cognitive Impairment. CLINICAL EEG and NEUROSCIENCE. 2009VOL 40N0 2

diagnosis and predictive utility of EEG in MCI and questionable dementia.	
7.Objective To compare differences in severity and type of electroencephalography (EEG) abnormalities between early and late onset Alzheimer's disease (AD) and to assess the influence of APOE genotype on this association, in order to understand the biological differences in AD according to age at onset Method Of 460 probable AD patients and 336 patients with subjective complaints, serving as controls, EEG and APOE genotype were obtained. Subjects were categorised by age into a younger (#65 years) and an older group (>65 years), based on age at diagnosis. Severity and type of EEG abnormalities were visually assessed. Severity of EEG abnormalities ranged from normal to slightly abnormal to moderately severe. EEG abnormalities were characterised as only focal abnormalities, only diffuse abnormalities or both focal and diffuse abnormalities. Results Logistic regression revealed that younger AD patients more often had EEG abnormalities, which were more severe, with a predominance of both focal and diffuse abnormalities. In controls, we observed the opposite, as older controls more often had EEG abnormalities than younger controls. Furthermore, APOE 34 negative AD patients had more severe EEG abnormalities than APOE 34 positive AD patients, while no such effect was observed in controls. There was no interaction between age at onset and APOE 34 genotype. Conclusion Early onset and APOE 34 negative AD patients present with more severe EEG abnormalities than late onset and APOE 34 positive AD patients. These results suggest that in younger patients, AD manifests with more prominent functional brain changes.	7.Hanneke de Waal, et al. EEG abnormalities in early and late onset Alzheimer's disease: understanding heterogeneity. J Neurol Neurosurg Psychiatry 2011;82:67e71
8. Andmebaasid: PubMed and Web of Science. The core CSF biomarkers of neurodegeneration (T-tau, P-tau, and Aβ42), CSF NFL, and plasma T-tau were strongly associated with Alzheimer's disease and the core biomarkers were strongly associated with mild cognitive impairment due to Alzheimer's disease. Emerging CSF biomarkers NSE, VLP-1, HFABP, and YKL-40 were moderately associated with Alzheimer's disease, whereas plasma Aβ42 and Aβ40 were not. Due to their consistency, T-tau, P-tau, Aβ42, and NFL in CSF should be used in clinical practice and clinical research.	8. Olsson, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016; 15: 673–84
9. Andmebaasid: Korea Med and international databases including Ovid-MEDLINE, EMBASE, and Cochrane Library. The purpose of this study was to carry out systematic review of the literature and metaanalysis to evaluate the diagnostic utility of cerebrospinal fluid (CSF) levels of the 42 amino acid form of amyloid-beta (Aβ1–42) as a biomarker for differentiating Alzheimer's disease (AD) from non-AD dementia. A total of 17 diagnostic evaluation studies were identified in which levels of CSF Aβ1–42 were assessed. Meta-analysis was performed on 11 robust studies that compared confirmed AD (n = 2211) with healthy individuals (n = 1030), 10 studies that compared AD with non-AD dementias (n = 627), and 5 studies that	9. Jin-A Mo, et al. Cerebrospinal Fluid β-Amyloid1–42 Levels in the Differential Diagnosis of Alzheimer's Disease—Systematic Review and Meta-Analysis. PLOS ONE | DOI:10.1371/journal.pone.0116802 February 24, 2015

compared amnestic mild cognitive impairment (n = 1133) with non-amnestic type subjects (n = 1276). Overall, the CSF Aβ1–42 levels were reduced in AD compared to controls or non-AD dementia. The effectiveness of test was evaluated for diagnostic accuracy (pooled sensitivity, 0.80 (95% CI 0.78–0.82); pooled specificity, 0.76 (95% CI 0.74–0.78). Reduced CSF Aβ1–42 levels are of potential utility in the differential diagnosis of AD versus non-AD dementias and controls. Diagnostic accuracy was high in AD versus healthy controls. However, differential diagnosis for MCI or non-AD might be evaluated by other biomarkers.	

Ravijuhendid

1.EFNS guidelines for the diagnosis and management of Alzheimer's disease. J. Horta, J. T. OBrienb, G. Gainottic, T. Pirttilad,, B. O. Popescue, I. Rektorovaf, S. Sorbig and P. Scheltensh on behalf of the EFNS Scientist Panel on Dementia

Elektoentsefalograafia (EEG) - võib aidata diferentseerida AT, subjektiivseid kaebusi ja psühhiaatrilisi haigusi. Soovitatud atüüpilise kliinilise pildiga AT korral. EEG võib anda infot varajase Creutzwald-Jacobi tõve (CJD), toksilis-metaboolse häire, võimaliku epileptilise amneesia või muu haiguse korral. AT haigetele on iseloomulik: vähenenud alfa laine, tõusnud teeta lained ja madalam keskmine sagedus. EEG võib olla normaalne kuni 14% AT haigetest. KUi EEG-s ainult difuussed muutused, siis see on pigem diagnoosi vastu. KUi esinevad nii difuussed kui ka fokaalsed nähud - AT või mõni muu dementsus.

Soovitus: EEG is recommended in differential diagnosis of atypical clinical presentations of AD (good practice point) and when CJD or transient epileptic amnesia is suspected (Level B).

Liikvori analüüs (*CSF analysis*) -Juhul, kui kahtlustatakse vaskuliiti, põletikulist, hematoloogilist või demüeliniseerivat haigust võui CJD – on liikvori uuring vajalik (pleotsütoos, valk, glükoos, valgu elektroforees). AT korral on liikvoris langenud beeta-amüloidi 42 tase (Ab42), samas kui tau-valgu või fosfo-tau hulk on tihti tõusnud. Ab42 sensitiivsus 86%, spetsiifilisus 90%; tau-valgu sensitiivsus 81%, spetsiifilisus 90%. Probleemiks on suur varieeruvus laborite vahel, mistõttu hetkel ei ole CSF hindamine usaldusväärne vahend.

Soovitus: Routine CSF analysis is recommended in differential diagnosis for atypical clinical presentations of AD (good practice point). CSF 14-3-3 or total tau measurement are recommended for the identification of CJD in patients with rapidly progressive dementia (Level B). Alterations in CSF total tau, phospho-tau and Ab42 support diagnosis of AD (Level B).

Geneetiline testimine – Seotud paljude eetiliste aspektidega. APP, PS1 ja PS2 geeni mutatsioonid seletavad 50% perekondlikest varase algusega AT-st. ApoE 4 alleel on ainuke geneetiline faktor, mis on seotud hilise algusega AT-ga, aga see ei pruugi tähendada tingimata haiguse avaldumist. Seetõttu ei ole alust soovitada Apo E4 testimist. Presümptomaatiline testimine perekondliku dementsuse korral tuleks läbi viia vaid patsiendi soovil ja spetsialiseeritud keskustes. Võib jälgida Huntingtoni tõve protokolli.

Soovitus: Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. Routine Apo E genotyping is not recommended.

Teised uuringud: Enamasti kliinilistes uuringutes, igapäevapraktikas ei kasutata. Mitte-närvikoe uurimine (fibroblastid, trombotsüüdud, vaskulaarne epiteel) - analüüsitakse DNA kahjustust ja parandamise mehanisme, autofaagiat, oksüdatiivset stressi, ioonkanaleid, intratsellulaarset Ca regulatsiooni jne. Naha ja lihasbiopsia – diagnoosimaks tserebraalset autosoom-dominantset arteriopaatiat koos subkortikaalsete infarktide ja leukoentsefalopaatiaga (CADASIL -*cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy*). Ajubiopsia – potentsiaalselt ravitava dementsuse kahtlusel (Infektsioon? Põletik?).

2. Guideline watch (APA 2007): practice guideline for treatment of patients with Alzheimer`s disease and other dementias.

EEG – ravijuhendis ei käsitleta.

Liikvori analüüs - On suhtelselt vähe uuritud liikvori biomarkerite kasutamist diagnostikas. Välja arvatud harvadel juhtudel (CSF 14-3-3 valgu määramine CJD korral; viirusentsefaliidi kahtlus, jne), pole piisavalt tõenduspõhisust soovitada neid rutiinses kliinilises praktikas.

Geenitestimine – Geenitestimine ei ole tavaliselt osa rutiinsest patsiendi käsitlusest. Eriti ei ole soovitav määrata ApoE4 mutatsiooni. ApoE4 on osa 19. Kromosoomist, mis on sagedamini leitav dementsetel eakatel, on seotud hilise algusega dementsusega nii positiivse pereanamneesiga kui ilma. Aga leidub ka tervetel eakatel – ei soovitata.
Perekondliku AT seotud geenid: APP (amüloid prekursor proteiin) - kromosoomis 21; PSEN1 (preseniliin 1) - kromosoomis 14, PSEN2 (preseniliin 2) - kromosoomis 1. Geenitestimine on kommertsiaalselt võimalik PSEN1 osas – mis leidub tihti perekondliku AT korral (avaldub enne 50-eluaastat). Kuna pole ennetavaid meetodeid, soovitatakse testimist ainult koos põhjaliku nõustamise ja interpretatsiooniga. Tuleks suunata spetsiaalsesse keskusesse.

3. Dementia: supporting people with dementia and their carers in health and social care Clinical guideline, NICE. Published: 22 November 2006 (viimane ülevaatamine 2015 märtsis).

Liikvorianalüüs tuleks teha, kui kahtlustatakse Creutzfeldt–Jakobi tõbe või mõnda muud kiiresti progresseeruvat dementsust.
EEG ei tohiks olla kasutusel kui rutiinne uurimismeetod dementsusega patsientidel. EEG tuleks kaaluda, kui on kahtlus deliiriumile, frontotemporaalsele dementsusele või CJD-le. Või neil, kel kaasub dementsusega krambisündroom.
Ajubiopsia kui diagnostiline meetod tuleb kõne alla väga valitud patsientidel, kel dementsus pn põhjustatud arvatavalt potentsiaalselt pöörduvast põhjusest ja diagnoosida ei ole muul moel võimalik.

4.The Diagnosis of Dementia due to Alzheimer's Disease: Recommendations from the National Institute on Ageing and the Alzheimer's Association Workgroup (2011); (Rec NIAAA)

EEG –ei käsitleta.
Biomarkerid AT diagnoosis – liikvori amüloid-beeta, tau ja fosforüleeritud tau määramine. Kvantitatiivne interpretatsioon – varieerub eri laborite vahel, standardiseerimine on vajalik. Rutiinses kliinilises praktikas ei soovita kasutada.

5.Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians (2014)

EEG- ei ole ravijuhendis käsitletud.
Liikvori analüüs - amüloid B1-42 ja tau valgu määramine ei ole soovitatud kliinilises praktikas.
Geeniuuringud – varase algusega dementsusega (<65.a.) patsiendid tuleks suunata spetsialistile, kes otsustab geneetilise testimise vajalikkuse ja võimalikkuse.

6.Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)

EEG – ei käsitleta

Liikvori uuringud - amüloid beeta 42 ja tau taset liikvoris ei soovitata kliinilises praktikas määrata. On osa uuringuprotokollidest, tuleb läbi viia kogemustega keskustest, kus on valideeritud tehnoloogia.