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TARJA MALM & DAVIDE TREVISAN (ED.)

8TH KUOPIO ALZHEIMER SYMPOSIUM

From translational research to biomarkers, treatment and prevention strategies
Kuopio, Finland, June 6-8, 2018

8th Kuopio Alzheimer Symposium

From translational research to biomarkers, treatment and prevention strategies

TARJA MALM (ED.)

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26

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ABSTRACT

The 8th Kuopio Alzheimer Symposium is organised by the University of Eastern Finland, Institute of Clinical Medicine – Neurology and the Doctoral Program in Molecular Medicine. The scientific program features new and inspiring research findings on neurodegeneration, diagnosis and prediction of Alzheimer's disease and other neurodegenerative diseases. It also brings an update on biomarker studies, new advances in imaging, disease models and prevention, population-based prevention studies. The Finnish Session "Memory Day" concentrates on memory problems in individuals in the working age, diagnostics.
This book contains the program and abstracts of the 8th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 6-8, 2018.

National Library of Medicine Classification: WL 358.5, WM 173.7, WM 220, WT 155

Medical Subject Headings: Memory; Memory Disorders; Neurodegenerative Diseases; Brain; Cognition; Cognition Disorders; Dementia; Alzheimer Disease; Diagnosis; Diagnostic Techniques; Primary Prevention; Diagnostic Imaging; Neuroimaging; Depression; Parkinsonian Disorders; Substance-Related Disorders; Neurology; Therapeutics; Biomarkers; Intestines; Gastrointestinal Microbiome; Costs and Cost Analysis; Diet; Exercise; Nutrition Therapy

Yleinen suomalainen asiasanasto: muisti; muistihäiriöt; muistisairaudet; neurodegeneratiiviset sairaudet; dementia; Alzheimerin tauti; Parkinsonin tauti; aivot; diagnostiikka; kuvantaminen; markkerit; ennaltaehkäisy; hoito; hoitomenetelmät; kognitio; kustannukset; liikunta; päihteet; ravitsemus; suolisto; suolistomikrobisto

Welcome to 8th Kuopio Alzheimer Symposium

Dear Friends and Colleagues,

It is our great pleasure to welcome you to the 8th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 6-8, 2018, and organized by University of Eastern Finland, Institute of Clinical Medicine - Neurology.

Alzheimer's disease has been identified as a global health priority, as the growing burden of the disease will challenge the current healthcare systems and national economies. Consequently, the disease mechanisms, prevention, early diagnosis and treatment of Alzheimer's disease have been under intense research. In its 8th time, Kuopio Alzheimer Symposium provides an outstanding forum to meet and learn from highly respected top-level speakers, who will spotlight the up-to-date and significant advances in research field of Alzheimer's disease and other neurodegenerative diseases. The 8 thKuopio Alzheimer Symposium will also be an excellent opportunity for the attendees to collaborate, network and exchange innovative ideas for future Alzheimer's disease and other neurodegenerative diseases research, biomarkers, treatment and prevention.

We are proud to present our exciting scientific program, which features new and inspiring research findings related to new insights into neurodegeneration, diagnosis and prediction of Alzheimer's disease and other neurodegenerative diseases: update on biomarker studies, new advances in imaging, disease models and translational medicine, technology-supported diagnosis and care, novel approaches towards prevention, population-based prevention studies, and novel approaches in clinical treatment studies. The program also includes a Finnish Session "Memory Day" targeted at health care personnel working with memory patients.

We warmly welcome you all to enjoy this inspirational scientific event and experience the Finnish early summer and the midnight sun!

Mikko Hiltunen, PhD
Professor
Chair of the Organizing Committee

Miia Kivipelto, MD, PhD
Professor
Co-Chair of the Organizing Committee

8TH KUOPIO ALZHEIMER SYMPOSIUM

Organized by

University of Eastern Finland, Institute of Clinical Medicine - Neurology

The Doctoral Program in Molecular Medicine

Chairpersons
Mikko Hiltunen, Miia Kivipelto
General Secretary
Annakaisa Haapasalo
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Tarja Malm
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Anne Remes
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Symposium Secretaries
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8th Kuopio Alzheimer Symposium

Program and abstracts

Contents

8th Kuopio Alzheimer Symposium

PROGRAM IN BRIEF

MUISTIPÄIVÄ (FINNISH MEMORY DAY)
Wednesday, June 6 | 12.00 - 17.00

I SESSIO – TIEDONKÄSITTELYPULMIEN MONET TAUSTAT JA NIIDEN SELVITTELY
Pj. Remes A.
Tiedonkäsittelypulmat – myös työikäisten ongelma, miten selvittelen?
Päihteet ja kognitiiviset ongelmat
Depressio ja alkavan muistisairauden erotusdiagnostiikka
II SESSIO – HYVÄÄ HOITOA J ATUKEA MUISTISAIRAALLE JA PERHEELLE
Pj. Hallikainen M.
Liikunta ja kognitio – Liikunta on öljyä aivoille
Muistisairauden ravitsemuksellinen ja lääkehoito tulevaisuudessa
Palvelujärjestelmähoidon tukena - miten kustannusvaikuttavaksi?
III SESSIO – SUOLISTO – UUDET AIVOMME
Pj. Koivisto AM.
Aivojen ja suoliston mikrobiston yhteistyö,
Parkinsonismi ja suolisto
Keskustelu ja päätössanat

THE MAIN SYMPOSIUM: FROM TRANSLATIONAL RESEARCH TO BIOMARKERS, TREATMENT AND PREVENTION STRATEGIES
Thursday, June 7 | 10.00 - 18.35 Chairs Hiltunen M, Kivipelto M.

KEYNOTE LECTURE 1: Highlights of clinical Alzheimer research
KEYNOTE LECTURE 2: Translational research in Alzheimer's disease
I SCIENTIFIC SESSION - Translational research of neurodegeneration in Alzheimer's disease and other neurodegenerative diseases
Chairs Malm T and Hiltunen M.
II SCIENTIFIC SESSION - New developments in diagnostic and predictive biomarkers in Alzheimer's disease and other neurodegenerative diseases
Chairs Remes A and Ingelsson M.

Friday, June 8 | 8.30 - 16.15

III SCIENTIFIC SESSION - New technologies in neurodegenerative diseases, including imaging, disease models and neuroinformatics
Chairs Rinne J and Koistinaho J.
IV SCIENTIFIC SESSION - Co-morbidities of neurodegenerative diseases
Chairs Haapasalo A and van der Flier W.

V SCIENTIFIC SESSION - Prevention and therapies of neurodegenerative diseases
Chairs Kivipelto M and Skoog I.

8th Kuopio Alzheimer Symposium

PROGRAM OF THE SYMPOSIUM

MEMORY DAY (in Finnish Muistipäivä)
Wednesday, June 6
The Finnish Session - Memory Day - program is targeted for researchers and health care professionals - nurses, doctors, psychologists and other personnel working with patients having cognitive problems or for researchers and health care professionals who study to improve their competence in memory disorders. **The program of the Memory Day on June 6 will be in Finnish.**

I Sessio - Tiedonkäsittelypulmien monet taustat ja niiden selvittely
Puheenjohtaja: Professori Anne Remes, Neurologia, OY ja OYS

11:00-	Ilmoittautuminen ja lounas
12:00-12:05	**Tervetulosanat** Professori Anne Remes
12:05-12:15	**Alustus** Kansanedustaja Merja Mäkisalo-Ropponen Muistiliitto ry:n hallituksen puheenjohtaja
12:15-12:45	**Tiedonkäsittelypulmat – myös työikäisten ongelma, miten selvittelen?** Johtava psykologi, PsyT Teemu Paajanen, Työterveyslaitos
12:45-13:10	**Päihteet ja kognitiiviset ongelmat** Neuropsykologi, FT Pekka Rapeli, Päihdepsykiatria, HUS
13:10-13:35	**Depressio ja alkavan muistisairauden erotusdiagnostiikka** Ylilääkäri, LT Risto Vataja, Psykogeriatria ja neuropsykiatria, HUS
13:35-13:45	**Keskustelu**
13:45-14:05	*Tauko*

II Sessio - Hyvää hoitoa ja tukea muistisairaalle ja perheelle
Puheenjohtaja: Tutkimusjohtaja, LT Merja Hallikainen, Aivotutkimusyksikkö, UEF

14:05-14:30	**Liikunta ja kognitio – Liikunta on öljyä aivoille** Professori Heikki Tikkanen, Liikuntalääketiede, UEF
14:30-14:55	**Muistisairauden ravitsemuksellinen ja lääkehoito tulevaisuudessa** Professori Hilkka Soininen, Neurologia, UEF
14:55-15:20	**Palvelujärjestelmä hoidon tukena - miten kustannusvaikuttavaksi?** Professori Katri Vehviläinen-Julkunen, Hoitotiede, UEF ja KYS
15:20-15:30	**Keskustelu**
15:30-15:50	*Kahvitauko*

III Sessio - Suolisto – uudet aivomme?

Puheenjohtaja: Professori Anne Koivisto, Neurologia, UEF ja KYS

15:50- **Aivojen ja suoliston mikrobiston yhteistyö**
16:20 Vastaava ylilääkäri, professori Juhani Ruutiainen, Neuroliitto

16:20-16:50 **Parkinsonismi ja suolisto**
Erikoislääkäri, LT Filip Scheperjans, Neurologia, HYKS

16.50-17.00 **Keskustelu ja päätössanat**
Professori Anne Koivisto

19:00- **Vastaanotto Kuopion kaupungintalolla**
Reception at Kuopio City Hall (Tulliportinkatu 31)

8th Kuopio Alzheimer Symposium

MAIN SYMPOSIUM

From translational research to biomarkers, treatment and prevention strategies

The program of the main symposium on June 7-8 is in English

Thursday, June 7

Opening and keynote session

Chairpersons: Mikko Hiltunen and Miia Kivipelto

09:00- Registration

10:00-10:05 **Opening words**
Mikko Hiltunen, Chair of the Organizing Committee

10:05-10:15 **Welcome address**
Jorma Palvimo, Vice-Dean of the Faculty of Health Sciences, UEF, Kuopio, Finland

10:15-10:30 **Welcome address**
Sirpa Pietikäinen, Member of European Parliament

10:30-11:15 *Keynote lecture 1* **: Highlights of clinical Alzheimer research**
Hilkka Soininen, University of Eastern Finland

11:15-12:00 *Keynote lecture 2* **: Converging approaches to the development of anti-apoE4 therapy**
Daniel Michaelson, Rabin Institute of Neurobiology, Tel Aviv University, Israel

12:00-12:10 **Neurocenter Finland – promoting neuroscience and innovation**
Mikael von und zu Fraunberg, Director of Neurocenter Finland, Kuopio, Finland

12:10-13:00 Lunch break

I Scientific session - Translational research of neurodegeneration in Alzheimer's disease and other neurodegenerative diseases

Chairpersons: Mikko Hiltunen and Tarja Malm

13:00-13:25 **Multiscale translational in vivo imaging in Alzheimers disease**
Vesa Kiviniemi, Oulu University Hospital, Finland

13:25-13:50 **PSEN1 mutant iPSC-derived model reveals severe astrocyte pathology in Alzheimer's disease**
Jari Koistinaho, Helsinki University / UEF, Kuopio, Finland

13:50-14:15 **NMDA receptors and calcium in early synaptic dysfunction**
Luísa Lopes, Instituto de Medicina Molecular, Lisbon, Portugal

14:15-14:40 **BACE-1 inhibitor CNP520 for prevention studies in Alzheimer's disease**
Ulf Neumann, Novartis Institute for Biomedical Research, Basel, Switzerland

14:40-15:05 **Early role of dipeptide repeat proteins in C9orf72 ALS/FTD**
Dieter Edbauer, DZNE, Munich, Germany

15:05-16:00 Coffee break

II Scientific session - New developments in diagnostic and predictive biomarkers in Alzheimer's disease and other neurodegenerative diseases

Chairpersons: Anne Remes and Martin Ingelsson

16:00-16:25 **CSF automated biomarker assays and their implication for Alzheimer's disease management**
Maryline Simon, Roche, Basel, Switzerland

16:25-16:50 **Novel CSF fragments of tau: candidate biomarkers for Alzheimer's disease and tauopathies**
Kina Höglund, University of Gothenburg, Sweden

16:50-17:15 **Improved discrimination between healthy control subjects and patients with cognitive decline by integrating ELISA and mass spectrometry-based cerebrospinal fluid biomarkers**
Martin Ingelsson, Uppsala University, Sweden

17:15-17:40 **Diagnostic and predictive markers of predementia AD: the EMIF-AD biomarker discovery study**
Pieter Jelle Visser, University of Amsterdam, the Netherlands

20:00-22:30 **Get-together party and poster session**
(Scandic Ballroom, Satamakatu 1)

Friday, June 8

III Scientific session - New technologies in neurodegenerative diseases, including imaging, disease models and neuroinformatics

Chairpersons: Juha Rinne and Jari Koistinaho

08:00- Registration

08:30-08:55 **Midlife insulin resistance and late-life cognition, brain amyloid accumulation, and cerebrovascular lesions**
Laura Ekblad, Turku University Hospital, Finland

08:55-09:20 **Clinical decision support in diagnosing neurodegenerative diseases**
Jyrki Lötjönen, Combinostics, Tampere, Finland

09:20-09:45 **The potential of low-cost tests for decision support in neurodegenerative diseases**
Mark van Gils, VTT Technical Research Centre of Finland Ltd, Finland

09:45-10:10 **3D human neural cell culture models of Alzheimer's disease: towards a cure-in-a-dish?**
Doo Yeon Kim, MGH/Harvard Medical School, Charlestown, MA, USA

10:10-10:35 **Zooming in on alpha-synuclein aggregation: imaging super-powers**
Tiago Outeiro, University Medical Center Gottingen, Germany

10:35-11:00 Coffee break

IV Scientific session - Co-morbidities of neurodegenerative diseases

Chairpersons: Annakaisa Haapasalo and Wiesje van der Flier

11:00-11:25 **Advances in Alzheimer's diagnosis; implications for clinical practice**
Wiesje van der Flier, University of Amsterdam, Netherlands

11:25-11:50 **NPH Dementia**

Ville Leinonen, UEF / Oulu University Hospital, Finland

11:50-12:15 **Idiopathic normal pressure hydrocephalus and Alzheimer's disease: differential diagnosis and co-occurrence**
Etsuro Mori, Tohoku University, Japan

12:15-12:40 **Quantifying dementia risk and prevention potential in clinical trials**
Alina Solomon, UEF / Karolinska Institutet, Stockholm, Sweden

12:40-13:05 **Common molecular mechanisms of Alzheimer's disease and Type-2 diabetes**
Mikko Hiltunen, UEF, Kuopio, Finland

13:05-14:00 *Lunch break*

V Scientific session - Prevention and therapies of neurodegenerative diseases
Chairpersons: Miia Kivipelto and Ingmar Skoog

14:00-14:25 **Multi-domain interventions to prevent dementia: from FINGER to World-Wide FINGERS**
Miia Kivipelto, Karolinska Institutet, Stockholm, Sweden

14:25-14:50 **Preclinical Alzheimer's disease - Implications for prevention and treatment**
Ingmar Skoog, University of Gothenburg, Sweden

14:50-15:15 **Prevention and therapy for neurodegenerative disease: Asian perspectives**
Christopher Chen, University of Singapore, Singapore

15:15-15:40 **Adherence to multidomain preventive interventions and experiences from real-life implementation**
Tiia Ngandu, National Institute for Health and Welfare, Helsinki, Finland

15:40-16:05 **New treatment strategies to fight Alzheimer's disease or waiting for Godot**
Nenad Bogdanovic, Karolinska University Hospital, Stockholm, Sweden

16:05-16:30 **Health economic aspects of dementia prevention**
Anders Wimo, Karolinska Institutet, Stockholm, Sweden

16:30-16:40 **Closing remarks**
Hilkka Soininen, UEF, Kuopio, Finland

Muistipäivä abstraktit

WEDNESDAY, JUNE 6

I SESSIO – TIEDONKÄSITTELYPULMIEN MONET TAUSTAT JA NIIDEN SELVITTELY

TIEDONKÄSITTELYPULMAT - MYÖS TY ÖIKÄISTEN ONGELMA, MITEN SELVITTELEN?

Teemu Paajanen, neuropsykologian erikoispsykologi, PsT
Työterveyslaitos

Koetut tiedonkäsittelyn vaikeudet ovat yleisiä työikäisillä. Subjektiivisia muistin tai keskittymisen vaikeuksia on jopa 17-30% alle 65-vuotiaista. Syyt koettujen tiedonkäsittelyn oireiden taustalla ovat moninaisia ja myös oireiden laatu ja vaikeusaste vaihtelevat. Tyypillisiä kognitiivisten oireiden taustasyitä työikäisillä ovat mm. mielialatekijät, uniongelmat, työuupumus ja alkoholi. Toisaalta työurien pidentymisen seurauksena myös etenevien muistisairauksien ja aivoverenkiertohäiriöiden esiintyvyys työikäisten joukossa kasvaa. Työelämän kognitiivisten vaatimusten kasvu on uusi kuormitustekijä, joka paitsi haastaa aivojen tiedonkäsittelyä myös lisää lievempien häiriöiden käytännön merkittävyyttä. Terveydenhuollon selvittelyihin ohjautuneiden työikäisten kognitiivisten pulmien selvitteleminen on erityisen haastavaa silloin kun oireet ovat lieviä, eivätkä minkään sairauden diagnostiset kriteerit selkeästi täyty. Tiedonkäsittelyn oireita selvittävällä kliinikolla tulisi olla ymmärrystä ihmisen kognition eri osa-alueista, sekä siitä miten erilaiset taustasyyt näissä tyypillisesti ilmenevät. Tiedonkäsittelyn vaikeuksia voidaan selvittää useilla eritasoisilla menetelmillä. Tärkein menetelmä on huolellinen haastattelu, jota täydennetään potilaan ja läheisen täyttämillä oirekyselyillä. Tiedonkäsittelyn häiriöitä voidaan karkeasti arvioida seulontatestien avulla. CERAD-tehtäväsarja on toimiva menetelmä vanhemmalla iällä alkavan Alzheimerin taudin tunnistamisessa, mutta työikäisten tiedonkäsittelyn vaikeuksien arvioinnissa se ei useinkaan ole riittävän herkkä eikä kattava. Erotusdiagnostiset kysymykset edellyttävät usein tiedonkäsittelyn häiriöiden laadun ja vaikeusteen arviointia, jolloin tarvitaan laaja neuropsykologinen tutkimus. Työikäisten kohdalla neuropsykologinen tutkimus on perusteltu myös siksi, että oireiden vaikutusta työssä selviytymiseen voidaan arvioida. Työikäisten muisti-tutkimushankkeessa (TSR-2018) selvitettiin työssä olevien henkilöiden kokemia tiedonkäsittelyn oireita ja niiden yhteyttä muihin kliinisiin oireisiin, kuten mielialatekijöihin ja uniongelmiin, sekä alkoholin käyttöön ja työkuormitukseen. Tutkimuksen perusteella kognitiiviset ja kliinisten oireet ovat voimakkaasti yhteydessä toisiinsa, mutta eivät niinkään suoriutumiseen lyhyissä kognitiivisissa testeissä. Tuotimme tutkimuksessa vertailuarvoja Työssä muistaminen-kysymyssarjalle, jotta sitä on tulevaisuudessa mahdollista käyttää koettujen kognitiivisten oireiden arviointityökaluna.

PÄIHTEET JA KOGNITIIVISET ONGELMAT

Pekka Rapeli
HYKS, päihdepsykiatria

Päihdehäiriöt vaihtelevat lievistä erittäin vaikeisiin, ja niillä voi olla merkittävä vaikutus henkilöiden kognitiiviseen toimintakykyyn. Päihteiden käytön kognitiivista vaikutuksista saadaan paras kokonaiskuva, kun k äytettyjä ainetta tarkastellaan keskushermostoon haitallisesti vaikuttavina myrkkyinä. Toisaalta runsaan päihteiden käytön haitallinen vaikutus kognitiivisen suoriutumiseen todetaan usein oletuksia vähäisemmäksi. Kognitiivisia häiriöitä ei aina ha vaita, vaikka päihdehäiriöön liittyisi aivojen toiminnallisia tai rakenteellisia muutoksia. Aivot siis onnistuvat usein suojaamaan kognitiivista suoriutumista. Selkeästi havaittavien kognitiivisten häiriöiden on todettu painottuvan niihin, joilla päihteiden käyttöön liittyy myös muita terveyshaittoja. Sukupuoli ja kognitiivinen reservikapasiteetti vaikuttavat nekin osaltaan päihteisiin liittyvien kognitiivisten häiriöiden kehittymiseen tai niiden palautumiseen raittiuden aikana. Yllämainituista tekijöistä muodostuva monen osuman -malli kuvaa, sitä miten ja miksi päihdehäiriön vaikutus kognitiivisen toimintakykyyn vaihtelee hyvin vähäisestä erittäin suureen. Esimerkkeinä nostetaan esille alkoholin, kannabiksen ja opioidien pitkäaikaisen ja runsaan käytön vaikutukset.

DEPRESSIO JA ALKAVAN MUISTISAIRAUDEN EROTUSDIAGNOSTIIKKA

Risto Vataja
HYKS Psykiatrian tulosyksikkö, Gero-neuro-päihdepsykiatrian linja

Vakavan masennustilan ja muistisairauden oireet ovat suurilta osin samat. Tällaisia oireita ovat mm. sosiaalinen vetäytyminen; kognitiivinen taantuminen; toimintakyvyn laaja-alainen lasku; käytösoireet, kuten levottomuus, negativismi tai ahdistunut käyttäytyminen; unirytmin särkyminen sekä painon lasku. Uusimpien tutkimusten mukaan rajankäynti masennuksen ja muistisairauden välillä on kuitenkin usein mahdotonta: masennus saattaa olla sekä Alzheimerin taudin riskitekijä, prodromaalioire että komorbidi tila. Lisäksi molemmilla sairauksilla on samoja vaskulaarisia riskitekijöitä, ja niiden patofysiologiassa on yhteisiä piirteitä. Kliinikoilla on keinoja erottaa masennus muistisairaudesta. Tärkein on hyvä anamneesi, ja enn en kaikkea tieto oireiden kehittymisen äkillisyydestä tai mahdollisesta reaktiivisuudesta rasittaville elämäntapahtumille. Ikääntyvien potilaiden masennusoireiden diagnostiikkaan ja seurantaan suunnitellut mittarit ovat myös hyödyllisiä. Vaikka masennus saataisiin onnistuneesti diagnosoitua ja hoidettua, kuuluu kognition seuranta mielialaoireiden lisäksi näiden potilaiden hyvään hoitoon erityisesti niillä potilailla jotka ovat masennukseen sairastuneet ensimmäistä kertaa vanhoilla päivillään. Masennus voi olla ensimmäinen oire alkavasta muistisairaudesta tai osa sellaisen riskitilaa. On mahdollista, että oireiden tehokas hoito hidastaa muistisairauden etenemistä näillä potilailla.

LIIKUNTA ON ÖLJYÄ AIVOILLE

Heikki Tikkanen
Liikuntalääketieteen professori, Kuopion Yliopistollinen sairaala

Liikunnan terveysvaikutusten osoittaminen alkoi sydän- ja verisuonisairauksien ehkäisystä. Liikunnan tutkimus levisi aineenvaihduntatutkimuksiin ja sen myönteiset vaikutukset todettiin erityisesti typpi 2 diabeetikoille. Kun diabeteksen todettiin pitkään kestettyään johtavan sydän- ja verisuonisairauksiin, oli ympyrä sulkeutunut. Liikunnan terveysvaikutusten tutkiminen keskittyi tähän ympyrään. Tuolloin aivot unohtuivat mutta nykyään aivotoimintojen ja liikunnan välisen yhteyden tutkiminen on iso alan tutkimussuuntaus.
Aivot muodostava vain noin 2 % kehon painosta mutta levossa ne kuluttava 20 % kehon energiasta. Tästä energiankulutuksesta 70-80 % kuluttaa aivosolut ja lopun muut aivosoluja ympäröivät solut. Lihaksisto muodosta noin 40 % elimistön painosta (ja energiankulutuksesta) mutta liikuntasuoritusten aikana lihaksisto muodosta valtaosan energiakulutuksesta ja sen läpi kulkee suurin osa myös verenkierrosta.
Aivojen toiminta, siihen liittyvä säätely ja liikunta ovat yhteydessä toisiinsa molempiin suuntiin. Perinteisesti ajatellaan, että aivojen merkitys liikunnassa tulee vain suorituksen käynnistäjänä, motorisen toiminnan aloittajana. Tämä onkin totta aivojen aktivaation kannalta mutta tällöin jää huomioimatta palaute (feed-back), joka muista kudoksista tulee aivoihin. Osa siitä on hermostollista palautetta mutta viimeaikainen tutkimus on osoittanut myös aineenvaihdunnallisen palautteen, erityisesti energia-aineenvaihdunnasta tulevan palautteen, olevan merkityksellistä.

Aivot käyttävät pääasiassa veren glukoosia energialähteenään. Ottaen huomioon aivojen suuren energiatarpeen, ne ovat jatkuvan verenvirtauksesta tulevan glukoosin varassa. Aivot voivat käyttää energialähteenä myös muuta kuin glukoosia. Ehkä yllättävin liikuntaan liittyvä linkki on maitohappo, laktaatti. Laktaattia muodostuu lihaksistossa glukoosin käytön seurauksena kun liikuntasuoritus on intensiivistä. Laktaatin tuoton on ajateltu liittyvä lihasväsymykseen (vaikka näin ei ilmeisesti olekaan). Viimeaikaiset tutkimukset ovat soittaneet että aivosolut käyttävät laktaattia energialähteenään, levossa noin 8 % mutta rasituksessa jopa 20% energiantuotosta. Yllättävin havainto on, että aivosolujen laktaatinkäyttö olisi yhteydessä pitkäaikaiseen muistiin.

Liikunta on siis öljyää aivoja siis monin tavoin: Verenkierron kautta, verisuoniterveyden kautta mutta se öljyää aivoja ilmeisesti suoraan myös (lihas)aineenvaihdunnan kautta viestittäen.

MUISTISAIRAUDEN RAVITSEMUKSELLINEN JA LÄÄKEHOITO TULEVAISUUDESSA

Hilkka Soininen
Institute of Clinical Medicine, neurology, University of Eastern Finland; Neurocenter, neurologoy, Kuopio University Hospital, Kuopio, Finland

Yleisin muistisairaus, Alzheimerin tauti on monitekijäinen – sekä geenit että elintavat vaikuttavat taudin syntyyn. Viime vuosina muistisairauksien ehkäisy on saanut lisääntyvää huomiota. Alzheimerin taudin hoitoon ei ole tullut uusia lääkkeitä markkinoille 20 vuoteen. Taudin syntyyn ja etenemiseen vaikuttavaa lääkettä on etsitty sekä perustutkimuksen että isojen kliinisten lääketutkimusten keinoin, mutta tehokasta lääkettä ei ole ei ole toistaiseksi löytynyt. Edelleen tutkitaan sekä oireisiin että taudinkulkuun vaikuttavia lääkkeitä mm. immunologisia hoitoja.

Mielenkiinto on kohdistunut myös ehkäisyn mahdollisuuksiin ja eniten tutkimustietoa on Alzheimerin taudissa. Myös aivoverenkierron sairauksiin liittyvää muistisairautta on mahdollista ehkäistä. Sen sijaan tällä hetkellä ei ole riittävästi tutkimustietoa mahdollisuuksista ehkäistä muita muistisairauksia kuten otsa-ohimolohkorappeumaa.

Varhaisen Alzheimerin taudin hoitoon kehitetyn kliinisen ravintovalmisteen vaikutusta hidastaa kognitiivisten toimintojen heikkenemistä tutkittiin EU-rahoitteisessa LiPiDiDiet-tutkimuksessa (Soininen ym. Lancet Neurology, 2017). Monikeskustutkimukseen, jota Suomen yliopisto koordinoi, osallistui 311 potilasta 11 keskuksessa. Osallistujilla oli tutkimuksen alkaessa varhaiseen Alzheimerin tautiin liittyvää lievää tiedollisten toimintojen heikentymistä. Heidät satunnaistettiin kahteen ryhmään, joista toinen käytti kahden vuoden ajan päivittäin kliinistä ravintovalmistetta ja toinen vertailuvalmistetta. Kliininen ravintovalmiste sisälsi muun muassa rasvahapoista ja vitamiineista koostuvan Fortasyn Connect -ravintoaineyhdistelmän.

Neuropsykologisella testisarjalla (NTB) ei voitu osoittaa merkitsevää eroa ryhmien välillä. Sen sijaan CDR-SB-yhdistelmämittarilla mitattava ajattelu- ja toimintakyky arjen tilanteissa heikkeni kliinisen ravintovalmisteen käyttäjillä 45 prosenttia vähemmän kuin vertailuryhmällä. Lisäksi kliinisen ravintovalmisteen käyttäjillä havaittiin vähemmän Alzheimerin tautiin liittyvää aivojen surkastumista. Hippokampuksen tilavuudessa eroa vertailuryhmään oli 26 prosenttia ja aivokammioiden tilavuudessa 16 prosenttia.

Tulokset lisäävät ymmärrystä ravitsemushoidon mahdollisuuksista Alzheimerin taudin varhaisvaiheessa.

PALVELUJÄRJESTELMÄ HOIDON TUKENA - MITEN KUSTANNUSVAIKUTTAVAKSI

Katri Vehviläinen-Julkunen
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Maassamme meneillään oleva ja viimeisiä poliittisia päätöksiä odottava sosiaali- ja terveydenhuollon (Sote) -uudistus tavoittelee hoidon vaikuttavuuden lisäksi kustannustehokasta sosiaali- ja terveydenhuollon palveluiden tuottamista. Uudistuksen perustana on vuonna 2010 v oimaan tullut Terveydenhuoltolaki (1326/2010), minkä tavoitteena on turvata väestölle laadukkaat, yhdenvertaiset ja asia kaskeskeiset palvelut. Palvelujärjestelmän toimissa korostetaan entistä enemmän tietoon ja monialaiseen näyttöön, evidenssiin perustuvaa toimintaan. Potilaiden hoidon, toimenpiteiden ja johtamisen vaikuttavuuden osoittaminen on keskeistä. Näin ollen entistä suuremmat vaateet liittyvät erityisesti sujuviin hoitoprosesseihin ja hoidon vaikuttavuuden sekä laadun ja potilasturvallisuuden edistämiseen.

Suomessa palvelujärjestelmän arviointia ja kehittämistä vauhdittaa väestön ikärakenteen nopea muutos, elintapoihin liittyvien pitkäaikaissairauksien lisääntyminen, teknologian kehitys, digitalisaatio sekä vahva potilas- ja asiakaskeskeisyyden korostus. Terveydenhuollossa edistetään hoitoprosessien sujuvuutta, hoito on hyvin kohdennettua ja täsmällistä, mikä näkyy mm. sairaaloiden hoitopäivien lyhentymisenä ja polikliinisten palvelujen lisääntymisenä. Kyseis et tekijät muokkaavat toimintaympäristöä ja aset tavat uusia osaamisvaatimuksia sosiaali- ja terveydenhuollossa työskenteleville ammattilaisille, johtajille, kouluttajille ja tutkijoille. Erityisen haasteellista on, että palvelujärjestelmässä käytettävissä oleva tieto sijaitsee useissa eri lähteissä ja rekistereissä. Lisäksi se on lähinnä menneisyyteen katsovaa. Olemassa olevien rekistereiden sisältämä tieto kuten sähköiset terveystiedot ja –tietoverkot sisältävät myös tärkeää kansanterveydellistä tietoa. Ns. big data mahdollistaa talouden hallinnan kehittämistä erilaisilla analysointitavoilla, joita ovat mm. koneoppiminen ja ennustava mallinnus. Tämä big data -an alytiikka on kehittymässä ja materiaalin analysointi mahdollistaa kustannustehokkaan ja kliinisesti paremman hoidon ja ennustettavuuden sekä vaikuttavuuden osoittamisen. Esimerkkinä palvelujärjestelmän kehittämisestä hoidon tueksi on Itä-Suomen yliopistossa tieteiden välisessä yhteistyössä kehitetty henkilöstömitoitustyökalu terveydenhuoltoon. Se auttaa sovittamaan henkilöstöresurssit potilaiden tarpeisiin kustannustehokkaasti potilas- ja henkilöstöjärjestelmien tietoja yhdistämällä.

AIVOJEN JA SUOLISTON MIKROBISTON YHTEISTYÖ

Juhani Ruutiainen
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Aivot ja suoliston mikrobisto keskustelevat keskenään. Suoliston mikrobistosta valtaosa on bakteereja, mutta mukana on myös arkkeja, viruksia ja tumallisia mikrobeja. Yhteyttä pidetään useamman kanavan kautta. Pisimpään tunnistetut kommunikaatioreitit ovat parasympaattinen ja sympaattinen tahdosta riippumaton hermosto sekä suoliston oma enteraalinen hermosto. Aivojen tunnetilat välittyvät mikrobistolle myös hormonaalisten signaalien kautta. Sanonta ”perhosia vatsassa” on monelle tuttu kuvaamaan esiintymisjännitystä. Bakteeristo puolestaan viestittää aivojen suuntaan aineenvaihduntatuotteillaan, jotka säätelevät keskushermoston toimintaa endokrinologisen ja immunologisen järjestelmän kautta. Aineenvaihduntatuotteet vaikuttavat joko suoraan suolinukan solujen reseptoreihin tai imeytyvät suoliston seinämän läpi systeemisen verenkierron puolelle keskushermoston ulottuville. Suoliston bakteerit kykenevät myös tuottamaan merkittäviä määriä keskushermoston toimintaan yhdistettyjä hermovälittäjäaineita kuten asetyylikoliinia, dopamiinia, gamma-aminovoihappoa, noradrenaliinia, serotoniinia ja niiden esiasteita. Ulkoiset tekijät kuten antibioottihoito, infektiotaudit, ruokavalion muutokset ja ympäristömyrkyt voivat johtaa suolen bakteerilajistojen epätasapainoon. Tällainen dysbioosi on alustavasti yhdistetty erilaisiin aivotauteihin kuten Alzheimerin tautiin, autistisen kirjon oireyhtymiin, MS-tautiin ja Parkinsonin tautiin. Osassa yhteys on ilmeinen, osassa tutkimustieto on ristiriitaista. Epäselvää on myös, muokkaavatko kyseiset sairaudet suolen bakteeristoa vai lisääkö dysbioosi alttiutta sairastua tai sairauden kliinistä aktiivisuutta kuten oireiden voimakkuutta tai etenemisnopeutta.

PARKINSONISMI JA SUOLISTO

Filip Scheperjans, LT
HUS Neurokeskus, Neurologian linja

Parkinsonin tauti on toiseksi yleisin hermoston rappeumasairaus ja sitä sairastaa n. 15.000 potilasta Suomessa. Taudin klassiset oireet ovat bradykinesia, lihasrigiditeetti, vapina ja tasapainohäiriöt. Tautiin liittyy kuitenkin myös laaja kirjo nk. ei-motorisia oireita, joista erityisesti suolisto-oireet esiintyvät varhain, jopa ennen motorisia oireita, ja vaikuttavat merkittävästi elämänlaatuun. Ummetukseen ja ärtyvä suoli–oireyhtymään liittyy suurentunut Parkinsonin taudin riski. Oireiden taustalla on enterisen hermoston neurodegeneraatio mikä aiheuttaa mm. peristaltiikan häiriöitä. Lisäksi suolen limakalvon suojatoiminnot ovat Parkinsonissa heikentyneet. Luento keskittyy Parkinsonin taudin ruuansulatuskanavan oireisiin ja miten ne vaikuttavat mm. potilaiden oraaliseen lääkehoitoon. Käydään myös läpi miten ruuansulatuskanavan oireita, erityisesti gastropareesi ja ummetus tulee huomioida potilaiden hoidossa. Lopuksi esitetään myös ajankohtaisia tutkimustuloksia suoliston mikrobiston ja Parkinsonin yhteyksistä. Parkinson potilailla on todettu poikkeavuuksia suolen mikrobiston koostumuksessa ja toiminnassa, mikä voi olla merkityksellistä taudin syntymekanismien ymmärtämiseen. Mikrobiston ja isännän vuorovaikutuksen ymmärtäminen Parkinsonin taudissa voi avata uusia mahdollisuuksia varhaisdiagnosoinnissa ja hoidossa.

Abstracts for Invited Talks

THURSDAY, JUNE 7

MAIN SYMPOSIUM

KEYNOTE LECTURE I

HIGHLIGHTS OF CLINICAL AZHEIMER RESEARCH

Hilkka Soininen

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Development of treatment and prevention are major challenges of Alzheimer's disease (AD) research. By using biomarkers diagnosis of AD can be made earlier and participants recruited into drug trials in earlier phase that is important when investigating effect of disease modifying treatments. Studies such as ADNI, EMIF, VPH-DARgggE, PredictND, JPND-BIOMARKADPD and genetic consortia have produced a huge amount biomarker data. Sequence of disease progression was also confirmed by DIAN reporting that in AD mutation carriers beta-amyloid starts accumulating over two decades before symptoms, metabolism declines six years later, and brain atrophy appears about five years before symptoms (Gordon et al Lancet Neurology 2018). Prevention and interventions towards modifiable risk factors of cognitive decline have gained worldwide interest. The FINGER study is the first large multimodal controlled trial in elderly individuals with increased risk of dementia showing that the multidomain lifestyle intervention protected against cognitive and functional decline. The lifestyle intervention involved nutrition counseling, physical exercise, cognitive training and managing cardiovascular factors (Ngandu et al Lancet 2015). In EU-funded LIPIDIDIET clinical trial patients with prodromal AD were randomised to receive either the nutritional intervention or control product for 24 months. The primary endpoint, impact on neuropsychological test battery, was not met. However, key secondary endpoints showed significant advantages for nutrient-treated patients with 45% less worsening in the Clinical Dementia Rating-Sum of Boxes. Furthermore, there was less brain atrophy in the active group, with 26% difference for the hippocampus and 16% for the ventricular volume (Soininen et al Lancet Neurology 2017).

KEYNOTE LECTURE II

CONVERGING APPROACHES TO THE DEVELOPMENT OF A NTI-APOE4 THERAPY

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Apolipoprotein E4 (apoE4), the most prevalent genetic risk factor for Alzheimer's disease (AD) differs from its AD benign isoform apoE3 by one nucleotide. Based on this difference we designed a CRISPR Cas9 variant based system that specifically targets and knockouts ApoE4. Application of this approach to mouse astrocytes expressing the human apoE3 or apoE4 gene led to a decrease in the levels of apoE4 protein (>56%) and DNA but had no effect on the corresponding apoE3 levels. We next focused on the apoE4 molecule. This was performed utilizing specific anti-apoE4 mAbs and by lipidation related pharmacological treatments. Repetitive i.p. immunization of young apoE4 targeted replacement mice resulted in the accumulation of apoE-IgG complexes in the brain and in reversal of the Aβ42, tau and of the associated synaptic impairments and cognitive deficits. ApoE4 is hypolipidated relative to apoE3. Treatment of young apoE4-targeted replacement mice with CS-6253 which is an agonist of the lipidation protein ABCA1 reversed the hypolipidation of apoE4 and the apoE4 driven brain and cognitive impairments. Additional in vitro mechanistic studies utilizing GFP labelled ABCA1 expressed in Hela cells and TIRF fluorescence microscopy revealed that apoE4 was associated with larger ABCA1 aggregates suggesting that the hypolipidation of apoE4 relative to apoE3 may be driven by its effects on the aggregation of ABCA1. In conclusion, the present animal model study has identified and defined novel spoE4 gene and protein related therapeutic approaches which now need to be translated to AD patients.

MULTISCALE TRANSLATIONAL IN VIVO IMAGING IN ALZHEIMER'S DISEASE

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Neurodegenerative diseases such as Alzheimer's dementia (AD) lack early diagnostic tools, effective treatment and cause about 1 billion € annual healthcare burden in Finland alone. Recent findings on AD propose that a malfunction of the brain clearance mechanism called glymphatic system leads to slow accumulation of proteins and finally, neuronal degeneration. Findings on AD mouse-models further indicate that increasing of blood brain barrier (BBB) permeability with focused ultrasound (FUS) can facilitate the removal of the protein accumulations and reverse memory loss. While the glymphatic system and factors increasing brain clearance are intensely debated, thorough investigation on their roles is needed to fully utilize the high therapeutic potential of manipulation of the (g)lymphatic system. OPEN-consortia (OY: Kiviniemi, Eklund, Myllylä, HU Alitalo) funded by Academy of Finland in Terva-call and JAES-foundation are doing translational research spanning from in vivo genetic mice multi-photon micro-scopy to human brain multimodal MREG imaging. Advanced opto-electronic brain monitoring is used to measure the status of glymphatic brain system at various manipulations of BBB. Investigation of tailored techniques for BBB opening should reveal the role of BBB permeability in brain clearance and allow optimization of therapies targeted to areas of its insufficiency. Current human research indicates novel approaches to MRI signal analysis can indeed find support for failure of the glymphatic clearance pulsations in early stage AD. Advances in opto-electronic imaging enable the monitoring of dynamic free water changes in the human brain that further support MRI imaging findings.

PSEN1 MUTANT IPSC-DERIVED MODEL REVEALS SEVERE ASTROCYTE PATHOLOGY IN ALZHEIMER'S DISEASE

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Rationale: Astrocytes are the most abundant non-neuronal cell type in the CNS and have multiple indispensable tasks in brain function, including energy supply to neurons in the form of lactate, as well as synapse formation and maintenance. Human astrocytes integrate 20 times more synapses and propagate Ca2+ waves far more quickly than their rodent counterparts. As astrocytes have been suggested to have a role in AD pathogenesis, we generated hiPSC-derived astrocytes from patients with AD carrying PSEN1-E9 mutation as well as healthy and gene-corrected isogenic controls, and characterized the astrocyte phenotype.

Methods: Somatic cells were reprogrammed to iPSCs with either lentiviral or Sendai virus vectors from three individuals carrying the PSEN1-E9 mutation and three healthy adult control individuals, all carrying the neutral ε3/ε3 isoforms of APOE. Gene- corrected isogenic control lines from PSEN1-E9 carriers were generated using CRISPR/Cas9 methodology. Astrocyte differentiation was carried out by a slightly modified protocol from the method published by Krencik et al. 2011.

Results: AD astrocytes showed robust accumulation of full-length PSEN1, while the enzymatic activity of γ-secretase was not changed. AD astrocytes manifested hallmarks of disease pathology, including increased Aβ production, altered cytokine release, and dysregulated Ca2+ homeostasis. Furthermore, due to altered metabolism, AD astrocytes showed increased oxidative stress and reduced lactate secretion, as well as compromised neuronal supportive function, as evidenced by altering synaptic Ca2+ responses in healthy neurons.

Conclusions: Our findings highlight the importance of astrocytes in AD pathology and demonstrate that hiPSC-derived astrocytes provide a valuable tool for studying AD disease mechanisms.

NMDA RECEPTORS AND CALCIUM IN EARLY SYNAPTIC DYSFUNCTION

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Synaptic dysfunction plays a central role in Alzheimer's Disease (AD), since it drives the cognitive decline (Selkoe, 2017, Ann Neurology; Walsh and Selkoe, 2004, Neuron). Indeed, in age-related neurodegeneration, cognitive decline has a stronger correlation to early synapse loss than neuronal loss in patients (DeKosky and Scheff, 1990, Ann Neurology). Despite the many clinical trials conducted to identify drug targets that could reduce protein toxicity in AD, such targets and strategies have proven unsuccessful. Therefore, efforts focused on identifying the early mechanisms of disease pathogenesis, driven or exacerbated by the aging process, may prove more relevant to slow the progression rather than the current disease-based models. Recently, an association between a polymorphism of the adenosine A2A receptor (A2AR) encoding gene - ADORA2A, with hippocampal volume (synaptic loss) in mild cognitive impairment and AD was reported (Horgusluoglu-Moloch et al, 2017, Neurobiol Aging). This polymorphism occurs in a non-coding region, upstream to the coding sequence and it was just suggested, but not studied, that it could imply alterations in A2AR expression. From animal studies, we know that A2AR expression in the hippocampus occurs upon aging (Lopes et al, 1999, J. Neurochem) and their activation induces glutamate release, calcium influx, leading to hippocampus-dependent cognitive deficits (Viana da Silva et al, 2016, Nat Comm). Moreover, several epidemiological studies have shown that regular consumption of caffeine - an adenosine receptor blocker - attenuates memory disruption during aging and decreases the risk of AD in humans (Eskelinen et al, 2009, JAD). I will share our latest data on the synaptic function of A2AR in age-related conditions. We have found a significant overexpression of A2AR in hippocampal neurons of aged human brain, which is aggravated in AD patients. A similar profile of A2AR overexpression - driven by the CaMKII promoter in rat forebrain neurons - was sufficient to mimic age-like memory impairments in young animals, and to induce a LTD-to-LTP shift in the hippocampus. This shift was due to an increased NMDA receptor gating, consequent activation of mGluR5 and increased Ca2+ influx. Importantly, we revealed a similar LTD-to-LTP shift in memory impaired aged rats and in APP/PS1 mice modeling AD, a phenotype that we rescued upon A2AR blockade. Our recent report of a similar mGluR5/A2AR involvement in the hippocampus, in the context of alpha-synuclein/Parkinson's disease (Ferreira et al, 2017, Nature Neuroscience), strongly favors this mGluR5/NMDAR aberrant recruitment mediated by A2AR, as a common and key event underlying calcium dysfunction in age-related cognitive deficits.

BACE-1 INHIBITOR CNP520 FOR PREVENTION STUDIES IN ALZHEIMER'S DISEASE

Ulf Neumann

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Background Stopping amyloid-β (Aβ) deposition by BACE-1 inhibition appears to be a promising strategy to treat Alzheimer's disease (AD), but treatment in established dementia stages was unsuccessful. We hypothesize that BACE-1 inhibitor treatment needs to start in early stage Aβ deposition, before the onset of significant neurodegeneration. Prevention treatment requires a compound with favorable safety and tolerability; we designed CNP520 to meet these requirements.

Materials and Methods CNP520 was designed and profiled in vitro, using animal pharmacological, pharmacokinetic and metabolism studies and underwent toxicological profiling with oral studies up to 39 weeks duration. Clinical Phase I and Phase IIa studies in healthy elderly volunteers established its safety, tolerability, and active dose range.

Results When designing CNP520, we specifically addressed potency, selectivity, brain penetration, and metabolism pattern. Free compound levels in the periphery are significantly lower than IC50 values for important off-targets. Robust Aβ reduction and reduced neuroinflammation was observed in animals. Toxicology studies have not raised major safety concerns; we did not observe effects on myelin, muscle spindles, retina, pigmented organs. Humans Phase I studies showed a dose- and time-dependent reduction of CSF Aβ, and a pharmacokinetic profile suitable for once-daily dosing. A 3-months study showed that CNP520 is safe and tolerated in a dosing range that result in 90% reduction of CSF Aβ.

Discussion The profile of CNP520 supports its use in prevention studies of AD. Clinical Phase II/III studies have been initiated, which test CNP520 in a cognitively healthy population of enhanced risk to develop symptoms of AD. Participants are included based on their age, carriers of APOE4 genotype, and for those carrying a single allele, elevated brain amyloid.

Conclusions CNP520 is suited for the use in prevention trials of AD, the ongoing Generation Study 1 and Generation Study 2 will test the concept of prevention treatment in AD.

EARLY ROLE OF DIPEPTIDE REPEAT PROTEINS IN C9ORF72 ALS/FTD

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Expansion of the (ggggcc)n repeat in C9orf72 is the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The repeat RNA is translated in all reading frames into five dipeptide repeat (DPR) proteins by an unconventional mechanism. It is still unclear how toxicity of the repeat RNA and the DPR proteins are driving neurodegeneration in patients. To elucidate the role of DPR proteins in ALS/FTD, we generated cellular and animal models expressing the DPR proteins individually. Poly-GA, the most abundant DPR species in patient brains, is neurotoxic in vitro and in mouse models. Cryo-electron tomography reveals that poly-GA aggregates sequester and inhibit the proteasome. Immunoassays detect DPR proteins in the CSF of presymptomatic mutation carriers many years prior to disease onset. Together the data indicate that early DPR expression contributes to the prodromal symptoms and disease progression of C9orf72 patients.

CSF AUTOMATED BIOMARKER ASSAYS AND THEIR IMPLICATION FOR ALZHEIMER'S DISEASE MANAGEMENT

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Rationale: Early diagnosis of AD is important to achieve the maximum benefit from therapeutic intervention. Currently, diagnosis is largely based on clinical symptoms and accurate and r eliable validated biomarkers are n eeded to cover that recognized unmet need. Today automated assays are available for quantitation of the Al zheimer's disease (AD) biomarker amyloid-beta (Abeta42) and Tau proteins (tTau and pTau) in cerebrospinal fluid (CSF).

Methods: CSF samples were obtained from 2 cohorts the Swedish BioFINDER, consisting of patients with mild cognitive impairment (MCI) and subjective cognitive decline, and the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort consisting of patients with subjective memory complaints, MCI, and AD. Analyses were conducted to assess concordance between biomarkers in BioFINDER CSF samples and visual read amyloid-PET images. The performance of each biomarker cut-off was validated using CSF samples from the ADNI cohort. The ability of CSF biomarker status to predict clinical progression was assessed in patients from the ADNI cohort, measured by the change in the Clinical Dementia Rating Sum of Boxes (CDR-SB) score from baseline to 24 months.

Results: (1) High concordance was observed between CSF biomarkers, measured by the Elecsys® immunoassay and amyloid-PET; (2) Patients classified into biomarker positive and negative groups showed significantly different rates of progression over 24 months.

Conclusions: These evidence highlight a potential role for the Elecsys® CSF biomarker assays in guiding the management of patients with suspected AD as an alternative to detect amyloid positivity in patient with mild cognitive decline being evaluated for AD and to predict future cognitive decline in MCI patients.

NOVEL CSF FRAGMENTS OF TAU: CANDIDATE BIOMARKERS FOR ALZHEIMER'S DISEASE AND TAUOPATHIES

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Rationale: Tau pathology is a hallmark of several neurodegenerative diseases, including Alzheimer's disease (AD). Standard cerebrospinal fluid (CSF) total-tau immunoassays bind to the mid-region measuring increased levels in some, but not all neurodegenerative taupoathies. Novel cleavage sites of tau have been identified in brain tissue but data on CSF is scarce and no cl eavage-specific antibodies are a vailable. We hypothesise that secreted fragments of tau may reflect disease specific cleavages of tau.

Methods: CSF samples were immunoprecipitated using antibodies specific for tau followed by MS analysis on a hybrid quadrupole/orbitrap MS instrument. Bottom-up analysis of trypsin-digested samples and top-down analysis of 'intact' samples were performed. We generated end-specific antibodies and ELISA or Simoa assays were developed. Finally, for each fragment, we evaluated the clinical relevance in CSF studies comparing the levels between AD and other tauopathies to healthy controls. We also present data on correlations to tau and Tau PET imaging.

Results: We have identified novel cleavage sites on tau in CSF and developed assay to specifically measure these fragments. T he initial clinical validation demonstrates a potential diagnostic value for some of the fragments and their link to tangle pathology.

Conclusions: We have demonstrated that antibody-based enrichment of tau followed by high resolution MS analyses allows for the identification of novel fragments of tau in CSF. Pilot studies confirm the feasibility of analysing these fragments both in patients with tauopathies and controls. The results presented will add to our current understanding on tau processing and tau pathologies.

IMPROVED DISCRIMINATION BETWEEN HEALTHY CONTROL SUBJECTS AND PATIENTS WITH COGNITIVE DECLINE BY INTEGRATING ELISA AND MASS SPECTROMETRY-BASED CEREBROSPINAL FLUID BIOMARKERS

Payam Emami Khoonsari (1), Ganna Shevchenko (2), Stephanie Herman (1), Julia Remnestål (3), RoseMarie Brundin (4), Malin Degerman Gunnarsson (4), Lena Kilander (4), Henrik Zetterberg (5), Peter Nilsson (3), Lars Lannfelt (4), Martin Ingelsson (4)*, Kim Kultima (1)*

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Rationale: Decreased cerebrospinal fluid (CSF) levels of amyloid-β42 (Aβ42) with increased levels of total tau (t-tau) and phospho-tau (p-tau) can detect Alzheimer's disease (AD) with a sensitivity of up to 95% and a specificity of up to 87%. We wanted to explore novel markers that could further improve the accuracy for disease detection.

Methods: We applied ELISA and mass spectrometry-based shotgun proteomics to investigate classical biomarkers and the CSF proteome in 76 patients with AD, 11 with frontotemporal dementia (FTD), 74 with mild cognitive impairment (MCI) and 45 non-demented control subjects. The MCI patients were followed for 4-9 years and 21 of these converted to AD, whereas 53 remained stable.

Results: Using multivariate modeling including cross-validation, the combined measure of Aβ42, t-tau and p-tau could detect AD with an area under receiver operating characteristic curve (AUROC) of 92% (vs. non-AD subjects) and MCI/AD converters with an AUROC of 93% (vs. non-AD subjects). However, the AUROC for recognizing non-demented controls was only 72% (vs. all other groups). By combining the classical CSF biomarkers with a selection of proteomics markers, the AUROC of discriminating AD from non-AD subjects increased to 93%, whereas MCI/AD converters could be distinguished with an AUROC of 96% (vs. non-AD subjects). Finally, non-demented controls could be recognized with an AUROC of 86% (vs. all other groups).

Conclusions: Our findings suggest that the addition of new biomarkers in a model based approach can improve the value of analyzing CSF to distinguish control subjects from patients with cognitive decline.

DIAGNOSTIC AND PRED ICTIVE MARKERS OF PREDEMENTIA AD: THE EMIF-AD BIOMARKER DISCOVERY STUDY

Pieter Jelle Visser

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Rationale: There is an urgent need for diagnostic and prognostic markers for Alzheimer's disease (AD) in the predementia stage. To address this challenge we have set-up the EMIF-AD Multimodal Biomarker Discovery study and tested the diagnostic and prognostic value of proteins in CSF and plasma, atrophy patterns on MRI and genetic markers.

Methods: We selected 1200 individuals with normal cognition, mild cognitive impairment (MCI) or mild dementia from 11 existing European cohort studies. We performed central proteomic, metabolomic, genomic, epigenomic and imaging analyses with existing samples and scans.

Results: We included 609 amyloid positive individuals (127 with preclinical AD, 307 with prodromal AD, and 175 with dementia) and 612 amyloid negative individuals (365 with normal cognition, 220 with MCI, and 27 with dementia). The average follow-up was 2.3 years. We will present data from the first MRI, plasma proteomics, CSF proteomics, and genomics analysis.

Conclusions: By combining existing data and samples it is feasible to perform large scale multimodality biomarker discovery analyses.

FRIDAY, JUNE 8

III SCIENTIFIC SESSION – NEW TECHNOLOGIES IN NEURODEGENERATIVE DISEASES, INCLUDING IMAGING, DISEASE MODELS AND NEUROINFORMATICS

MIDLIFE INSULIN RESISTANCE AND LATE-LIFE COGNITION, BRAIN AMYLOID ACCUMULATION, AND CEREBROVASCULAR LESIONS

Laura Ekblad (1), Sini Toppala (1,2), Jyrki Lötjönen (3), Mira Karrasch (4), Jarkko Johansson (5), Semi Helin (1), Pauli Puukka (6), Hanna Laine (2,7), Antti Jula (6), Matti Viitanen (2,8), Juha O. Rinne (1,9).

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Rationale: Insulin resistance (IR) is a risk factor for cognitive decline, and IR is suggested to play an important role in the pathophysiology of Alzheimer´s disease (AD). Midlife seems to be a crucial time for measuring vascular risk factors to predict dementia. However, the associations among midlife IR and late-life cognitive performance, cerebrovascular lesions, and brain amyloid accumulation remain unknown.

Methods: Altogether 60 individuals without dementia (mean age 71 years) underwent neuropsychological testing, magnetic resonance imaging, and Pittsburgh compound B (PIB) PET imaging in 2014-2016. The volunteers were recruited based on their Homeostatic Model of Insulin Resistance (HOMA-IR) in the year 2000. 30 individuals had elevated HOMA-IR in midlife (IR+ group, HOMA-IR>2.17), and 30 had normal HOMA-IR (IR- group, HOMA-IR<1.25). The HOMA-IR cut-offs were based on the highest and lowest tertile of HOMA-IR in the Finnish Health 2000 Survey (n=5935). Both groups were enriched for APOEε4 carriers, resulting in 15 APOEε4 carriers per group.

Results: 60.0% of the IR+ group and 33.3% of the IR- group had an amyloid positive PET scan (odds ratio 3.0, 95% confidence interval 1.1-8.9, p=0.04). The IR+ group had lower executive function (p=0.019) and processing speed (p=0.006) test scores than the IR- group. The IR groups did not differ in cerebrovascular lesions (p=0.83).

Conclusions: These results indicate that midlife insulin resistance is an independent risk factor for brain amyloid accumulation and cognitive function in elderly individuals without dementia. Unexpectedly, individuals with insulin resistance did not have more cerebrovascular lesions than those without.

CLINICAL DECISION SUPPORT IN DIAGNOSING NEURODEGENERATIVE DISEASES

Jyrki Lötjönen (1), Juha Koikkalainen (1), Hanneke Rhodius-Meester (2), Marie Bruun (3), Marta Baroni (4), Timo Urhemaa (5), Daniel Rueckert (6), Jan Wolber (7), Lennart Thurfjell (1), Jean Georges (8), Juha Pärkkä (5), Mark van Gils (5), Anne Remes (9), Patrizia Mecocci (4), Wiesje van der Flier (2), Steen Hasselbalch (3) and Hilkka Soininen (9)

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Rationale: Diagnosing neurodegenerative diseases is not simple. Clinicians need to assess information from multiple sources and to evaluate based on their expertise the underlying reason behind symptoms. In the PredictND European research project, we have developed tools for helping clinicians to interpret all the data in a systematic and more objective way.
Methods: The PredictND project developed a clinical decision support tool including two main components. The image quantification module provides a rich set of imaging biomarkers from MRI images. The decision support module compares all the patient data to data from a high number of previously diagnosed patients. The tool measures how similar the patient being studied is either to different etiologies (Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia or cognitively normal) or to patients that progress to dementia. In PredictND, we validated the tool both in a prospective study of 800 patients from four memory clinics and in different studies with retrospective data.
Results: The key result of the prospective study was that the tool improves the confidence of clinicians in making decisions. Statistically significant difference was not, however, observed in diagnostic accuracy. Multiple PredictND studies showed that automatically computed imaging biomarkers combined with other data provide valuable information both for differential diagnostics and prediction of disease progression.
Conclusions: The PredictND project demonstrated that clinical decision support systems based on modern machine learning techniques can be useful in helping to interpret patient data in clinical practice.

THE POTENTIAL OF LOW-COST TESTS FOR DECISION SUPPORT IN NEURODEGENERATIVE DISEASES

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Rationale: There is a great need to detect onset of dementia as early as possible. This can help to provide treatments earlier, which may reduce costs and prolong maintenance of quality of life. For this, we need novel low-cost biomarkers that can be measured during daily living.
Methods: We concentrated on: web-based cognitive testing using the Muistikko test, computer games, and gait analysis. We compared the relationship of these measures with standard neuropsychological assessments used in clinical practice. As there is no efficient composite score for separating healthy, MCI and dementia cases, we developed a global cognitive score (GCS) composed of age, sex, MMSE, and different cognitive tests. Then, regression models were developed to estimate GCS from Muistikko- and computer-game features respectively. For the gait analysis, we studied time- and frequency features from 3D-accelerometry and performed correspondence analysis with established cognitive measures. Over 300 patients from four memory clinics in Europe (Amsterdam, Copenhagen, Kuopio and Perugia) participated in the context of the PredictND EU project.
Results: Both Muistikko test and game-based features show a good correspondence with the GCS. Additionally, gait-extracted features, such as speed, variance and regularity show correlations with different levels of cognitive impairment.
Conclusions: Low-cost measurements, that can be done easily during daily living, contain valuable information related to cognitive impairment. As such, they hold promise to give indications of risk of cognitive decline in early informal settings, thereby enrichening the existing set of tools we have at hand for decision support in dementias.

3D HUMAN NEURAL CELL CULTURE MODELS OF ALZHEIMER'S DISEASE: TOWARDS A CURE-IN-A-DISH?

S.S. Kwak, E. Brand, K.J. Washicosky, J. Park, D. von Maydell, K. Brenner, J.L Aronson, E. Bylylkabashi, S.H. Choi, R.E. Tanzi, D.Y. Kim

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Recently, we developed a 3D human neural culture model that produces robust A² aggregation and NFT-like tau aggregation. We found that Matrigel-based 3D culture system accelerated the aggregation of pathogenic Aβ species (Aβ plaques) and more importantly, induced accumulation of silver-positive and detergent-insoluble hyperphosphorylated tau protein (NFTs). In this presentation, I will explain a basic concept of our 3D culture models of AD and briefly show the recent progress, including (1) improved 3D culture models based on single-clonal hNPCs and microfluidic devices, (2) addition of neuroinflammatory elements using a microfluidic 3D human neuron/astrocyte/microglia co-culture system and (3) mechanistic studies to dissect pathogenic cascade that medi ates Aβ-induced tau phosphorylation. I will also show an update on our exploratory AD drug screening project using modified 3D culture model of AD in 96-/384-well plate format. Currently, we finished primary screening of 2460 drug library containing all the FDA-approved drugs and found 39 hits that strongly decrease accumulation of insoluble hyperphosphorylated tau with or without affecting Aβ accumulation.

ZOOMING IN ON ALPHA-SYNUCLEIN AGGREGATION: THE POWER OF NOVEL IMAGING APPROACHES

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Rationale: Parkinson's disease (PD) is t he second-most common neurodegenerative disorder, affecting 2-3% of the population over 65 years of age. Neuronal loss in the substantia nigra and intracellular protein inclusions containing misfolded ±-synuclein (aSyn) are the neuropathological hallmarks of PD. Thus, the aggregation of aSyn is tightly associated with neurodegeneration, and the current hypothesis is that aSyn propagates in a prion-like manner throughout the brain, and perhaps even from peripheral tissues. Although this hypothesis is fascinating, and could eventually open new therapeutic avenues aimed at preventing such spreading, there is still no definitive proof for the trans-neuronal spread of aSyn aggregates. Until recently, available imaging techniques did not allow the visualization of the 3D-architecture of the brain at a cellular resolution.
Methods: However, we now have available several techniques for tissue clearing in which whole organs are rendered macromolecule permeable and optical ly transparent, thereby exposing their cellular structure with intact connectivity. Other techniques allow us to overcome the diffraction limit for optical microscopes, and enable us to ima ge stained objects with nanoscale precision and thus higher resolution.
Results: We are applying these novel imaging techniques to zoom in on aSyn aggregation and spreading, in cells and in the mouse brain.
Conclusions: Ultimately, we expect that the use of these novel approaches may shed new light into the molecular mechanisms underlying PD and other synucleinopathies.

ADVANCES IN ALZHEIMER'S DIAGNOSIS; IMPLICATIONS FOR CLINICAL PRACTICE

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The advances in diagnosis of AD using MRI, markers in Cerebrospinal Fluid (CSF), and amyloid-imaging using PET are among the largest successes of AD research. Nonetheless, in a large proportion of patients, a diagnosis is only made in a late disease stage. A better and earlier diagnosis would be very beneficial, as with timely diagnosis, patients can receive help quicker and more effectively. ABIDE is a Dutch project that aims to improve AD diagnosis in memory clinics, by promoting effective application of MRI, CSF, and PET for diagnosis of MCI and AD in memory clinics, taking into account patients' perspective and wishes on their use. PredictND is a European project that aims to develop a clinical decision support system to integrate the wide array of diagnostic test results. In this lecture, innovations in diagnosis will be discussed with a focus on practical implications at everyday memory clinics. Focus groups with patients, caregivers and professionals provide support for the notion that decisions on diagnostic testing should be made in a setting of shared decision making. The predictND tool serves to integrate data from many different tests, allowing the clinician to weigh and combine all test results, supporting the clinician to arrive at a balanced diagnostic decision. In the context of ABIDE, we developed individualized risk models that allow estimation of probabilities of progression from MCI to dementia, taking into account patients' characteristics. The risk models will be integrated in an easy to use app, called the ADappt. Patients and caregivers also stress that they would value more specific information on what diagnostic test results mean for them. The ADappt therefore provides support for the diagnostic conversation, aiming to improve doctor-patient communication. With the development of new diagnostic tests, we enter an era where we can actually start to translate findings from science to everyday clinical practice. Tools to support the diagnostic process, may act as a catalyst for quicker and more effective diagnosis.

NPH DEMENTIA

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Rationale: Ventricular enlargement may indicate neurodegenerative disease like Alzheimer's disease (AD) but especially with simultaneous gait difficulty and obliterated parasagittal sulci, normal pressure hydrocephalus (NPH). Thus, patients with enlarged ventricles often manifest cognitive deterioration but the final specific diagnosis varies. Furthermore, patients with NPH may develop later comorbid other neurodegenerative disease. We aim to evaluate long-term cognitive outcome in patients with enlarged ventricles and clinically suspected NPH.

Methods: Kuopio NPH Registry (www.uef.fi/nph) includes over 900 patients with enlarged ventricles and possible iNPH with clinical characteristics, neuroradiological findings and frontal cortical brain biopsy. The patients are follow-up until death.

Results: In long-term follow-up, the demented population comprised 73% of non-shunted patients with enlarged ventricles, 63% of shunted iNPH patients that did not respond to treatment, and 46% of iNPH patients that were initially responsive to shunting. Based on our registry, we can estimate the following cognitive outcome of shunted iNPH patients. Approximately 25% remain cognitively intact, 25% will suffer mild cognitive impairment, 20% will have AD dementia, 20% vascular dementia, 10% NPH-related dementia and occasional cases will have FTD, PSP, CBD, LBD, PDD, ALS or MSA.

Conclusions: Dementia caused by various neurodegenerative diseases was frequently seen in patients with ventricular enlargement emphasizing a careful diagnostic evaluation in collaboration with neurologists and neurosurgeons. Furthermore, also patients with shunted iNPH need clinical follow-up and testing of shunt patency in case of deterioration.

IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS AND ALZHEIMER'S DISEASE: DIFFERENTIAL DIAGNOSIS AND CO-OCCURRENCE

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Idiopathic normal pressure hydrocephalus (iNPH) is a cause of cognitive impairment as well as gait disturbance and urinary symptoms in elderly adults that may resemble other disorders among elderly including Alzheimer's disease (AD), Lewy body dementia, and so on. The prevalence of iNPH is substantially high; population-based epidemiological studies carried out recently in Japan and Sweden demonstrated the prevalence of possible iNPH was around 2% in the elderly population. The only effective treatment for iNPH is CSF diversion with ventriculo-peritonal (VP) or lumbar subarachnoid space-peritoneal (LP) shunt. Several prospective cohort studies demonstrated benefits of VP shunt, and SINPHONI-2 carried out in Japan, a randomized controlled trial comparing shunt to conservative therapy, clearly demonstrated benefits of LP shunt. However, patients with iNPH are often misdiagnosed and inadequately treated. It has been recognized that a characteristic deformity called as Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH), which is apparent on MRI or CT, is a simple but valuable biomarker to differentiate iNPH from AD and to predict shunt-effectiveness. On the other hand, iNPH and AD often co-occur, and co-occurring AD may reduce the effect size of shunt surgery. It is to be determined whether shunt is beneficial for such patients. In any event, the effect size of shunt surgery in iNPH patients might be larger than that of drug treatment we now have and are expecting to have in AD patients. Finally, iNPH is an ideal model of dementia cure in a simple conceptual manner, which would provide a useful clue when considering the effect of developing AD treatments.

QUANTIFYING DEMENTIA RISK AND PREVENTION POTENTIAL IN CLINICAL TRIALS

Alina Solomon

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Rationale: Early identification of individuals with increased risk for dementia and who are most likely to benefit from interventions is essential for effective dementia prevention.
Methods: Recent systematic literature reviews have identified over 50 different prediction algorithms / risk scores for dementia developed during the past decade. This presentation will focus primarily on dementia risk scores that have already been used as practical tools for various purposes in clinical trials.
Results: Available dementia risk scores can be based on: 1) non-modifiable risk factors only (eg age, genetics); 2) modifiable risk factors only (eg lifestyle-related, vascular, metabolic and other manageable comorbidities); and 3) combinations of modifiable and non-modifiable risk factors. All 3 types of risk scores have been used in dementia prevention trials testing pharmacological or non-pharmacological interventions with varying results. So far the most successful intervention model has been lifestyle-based, ie multidomain interventions targeting real-life multifactorial risk profiles instead of a single risk factor.
Conclusions: Only a few studies have so far attempted to bridge the gap between dementia prediction and prevention. There is a clear need for validated prediction tools in both clinical trials and everyday practice to help health care providers identify at-risk individuals and direct them to the interventions that they are most likely to benefit from. It is also essential to develop prediction tools that estimate not only the risk for dementia but also an individual's prevention potential.

COMMON MOLECULAR MECHANISMS OF ALZHEIMER'S DISEASE AND TYPE-2 DIABETES

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Rationale: It is well-established that the risk for Alzheimer's disease (AD) is increased by type 2 diabetes (T2D). Several post-mortem studies have revealed insulin resistance in the AD brain, which have led to the suggestion that AD represents a 'type 3 diabetes'. Despite these links, the common underlying molecular mechanisms between AD and T2D are still elusive.

Methods: Large population-based cohorts METSIM (METabolic Syndrome In Men) and FINGER (Finnish Geriatric Intervention study to prevent cognitive impairment and disability) were used to elucidate AD-associated genetic determinants in relation to cardiovascular health- and metabolism-related parameters. Moreover, wild-type (WT) and APP/PS1 mice treated with intranasal insulin were used to elucidate the effects on insulin signaling pathway and tau in the brain.

Results: Carriers of protective *APP* A673T variant identified from METSIM cohort encompassed on average 30% lower levels of Aβ40 and Aβ42 in plasma as compared to the controls without any changes in the metabolic or cardiovascular traits. The assessment of peripheral effects of *APOE ε4* in METSIM and FINGER cohorts revealed a robust association with decreased levels of plasma high-sensitivity C-reactive protein (hs-CRP). Importantly, reduced hs-CRP levels and plasma Aβ42 showed an association independently of the *APOE* status. Finally, intranasal insulin treatment specifically activated hippocampal Akt2 kinase and its downstream signaling in WT, but not in APP/PS1 mice.

Conclusions: These results reinforce the suitability of large population-based cohorts in assessing the peripheral effects of AD-associated genetic variants and emphasize the disadvantageous link between AD-associated genetic components and insulin signaling in the brain.

V SCIENTIFIC SESSION - PREVENTION AND THERAPIES OF NEURODEGENERATIVE DISEASES

MULTI-DOMAIN INTERVENTIONS TO PREVENT DEMENTIA: FROM FINGER TO WORLD-WIDE FINGERS

Miia Kivipelto, On behalf of the World-Wide FINGERS network
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Rationale: Given the multifactorial etiology of dementia, multi-domain preventive interventions targeting several risk factors and mechanisms simultaneously are most likely to be effective.
Methods: This presentation gives an overview of recent multimodal lifestyle dementia prevention trials and discusses future directions in the field.
Results: The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is the first large trial showing that a multi-domain lifestyle intervention may prevent cognitive impairment. New results from the trial will be presented. The ongoing MIND-AD project (Multimodal preventive trials for Alzheimer Disease: towards multinational strategies) is testing the FINGER intervention model in patients with prodromal Alzheimer disease and lifestyle/vascular risk factors. FINGER represents a pragmatic model, which is now also being tested in diverse populations and settings (Europe, USA, China, Singapore, and Australia). To promote synergy across these trials and optimize efforts towards dementia prevention, we recently launched the World-Wide FINGERS Initiative. WW-FINGERS is an interdisciplinary network, to share experiences and data, and plan joint initiatives focusing on dementia prevention.
Conclusions: There is increasing evidence that it is possible to prevent or postpone late-life cognitive impairment and dementia with multi-domain lifestyle interventions. WW-FINGERS will facilitate synergistic use of data from several countries, creating a unique opportunity for rapid implementation of knowledge and definition of effective and feasible prevention programs for diverse populations.

PRECLINICAL ALZHEIMER'S DISEASE - IMPLICATIONS FOR PREVENTION AND TREATMENT

Ingmar Skoog

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Several studies suggest that midlife vascular risk factors, such as high blood pressure, high cholesterol, diabetes mellitus, atrial fibrillation and myocardial infarction, and factors such as leisure intellectual and physical activities, cardiovascular fitness, and dietary habits may influence risk of late-life Alzheimer's disease. Other mid-life factors, such as proness to stress, number of adverse life events, neurotic personality, and lower education are also among risk factors for late-onset Alzheimer's disease. Many of these risk factors are potentially preventable or modifiable. However, prevention trials so far are inconclusive. Several longitudinal population studies thus report that midlife high blood pressure and higher BMI are related to late onset AD. However, blood pressure and BMI starts to decline 5-10 years before onset of the disease. The explanation may be that AD changes in the brain may influence regulation of blood pressure. However, these factors might also be the result of very early AD changes in the brain, as there is evidence from brain imaging and neurochemical studies that AD changes are present more than two decades before the clinical onset of the disease. Indeed, among cognitively normal 70-year-olds, 23% had pathological cerebrospinal fluid beta-amyloid-42, 33% pathological tau and 10% pathological phospho-tau. In total, 46% had at least one pathological Alzheimer marker. Thus, the association between biological markers for AD and risk factors for the disease needs to be clarified to understand when prevention and treatment needs to be initiated.

PREVENTION AND THERAPY FOR NEURO DEGENERATIVE DISEASE: ASIAN PERSPECTIVES

Christopher Chen

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A recent report from the Lancet Commission on Dementia Prevention, Intervention and Care listed 9 potentially modifiable risk factors for dementia. Factors which may be relevant to lifestyle interventions in later life such as so cial isolation with a rela tive risk (RR) of 1.6, smoking with a RR of 1.6, diabetes with a RR of 1.5 and physical inactivity with a RR of 1.4 were calculated to have a weighted population attributable fraction (PAF), an estimate of the proportion of cases of dementia that could be avoided if exposure to specific risk factors were elim inated, of 2.3%, 5.5%, 1.2% and 2.6% r espectively. Measures to improve such factors may be beneficial, hence trials on multi-domain lifestyle interventions such as the recent FINGER study should be replicated globally. As part of the World Wide FINGER initiative, a pilot SINgapore GERiatric intervention study to reduce physical frailty and cognitive decline (SINGER) will be performed to establish the most appropriate multidomain lifestyle interventions for Singaporean seniors, optimise recruitment procedures and hence provide a strong basis for a proposed 2 year randomised controlled clinical trial. Other novel Asian approaches to therapy for Alzheimer's Disease include Traditional Chinese Medicines (TCM). An exemplar is t he ongoing Alzheimer's disease THErapy with NEuroaid (ATHENE) Study, a randomized, double blind, placebo controlled trial will assess the safety and efficacy of Neuroaid II in patients with mild to moderate Alzheimer's Disease stable on AChEIs or Memantine. Neuroaid II has neuroprotective and neuroproliferative properties in cellular and animal models of brain injury. Furthermore, Neuroaid is a possible modulator of amyloid precursor protein (APP) processing and tau hyperphosphorylation. It has shown favourable effects on cognitive function in AD patients with better tolerability and safety profile than standard AChEIs.

ADHERENCE TO MULTIDOMAIN PREVENTIVE INTERVENTIONS AND EXPERIENCES FROM REAL-LIFE IMPLEMENTATION

Tiia Ngandu

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Lifestyle interventions can be demanding for the participants. Participants must be adequately adherent to the trial protocol to achieve lifestyle changes that will provide cognitive benefit. Currently there is no golden standard for defining good or poor adherence, and in practice there is probably a dose-response relation between adherence and intervention outcome. Very little is known about adherence to non-pharmacological interventions. Characteristics of both the intervention and of the participant may affect adherence, and recent results from European lifestyle trials have identified potential determinants of adherence. Implementation of dementia prevention activities from trial setting into real-life is needed. Some of the key issues in planning implementation activities include identifying target groups for the interventions, identifying facilitators and barriers to achieve and maintain healthy lifestyle changes; and close collaboration with the key stake-holders responsible for the implementation activities. Experiences from an ongoing work to develop an operational model for the implementation of dementia prevention activities will be presented.

NEW TREATMENT S TRATEGIES TO FIG HT ALZHEIMER'S DISEASE OR WAITING FOR 'GODOT'?

Nenad Bogdanovic

1)Professor 2)Senior neurogeriatrician 3) Head of The Aging Brain , Theme Aging, Karolinska University Hospital, Stockholm Sweden

An effective treatment for Alzheimer's Disease (AD) is perhaps the greatest unmet need facing modern medicine. Approved drugs marketed in Scandinavia are the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. They are indicated for mild-to-severe AD or moderately-severe-to-severe AD, respectively. The effects of acetylcholinesterase inhibitors have been statistically small. The amyloid cascade hypothesis has dominated the specialty for the past two decades, with an emphasis on Aβ pathways, but tau and small molecules are also the focus of investigation. The diagnostic targets for new drugs include at-risk populations (prevention) and preclinical or pre-symptomatic AD, prodromal AD (ie, mild cognitive impairment due to AD), or mild-to-moderate AD. Disruption of the amyloid pathway is thought to be among the earliest targets for vaccines and antibodies to Aβ, and inhibitors and modulators of γ-secretase and β-secretase. Although link between Aβ deposition and tau remains unclear, the downregulation of tau-related toxicity might be of clinical benefit. Problem in developing drugs for AD dementia is the multifactorial nature of dementia, physical comorbidity in old individuals, including concurrent vascular dementia and different types of neurodegenerative lesions. While waiting for 'Godot', individualization and adjustment of current AChE related therapy to age, gender and APOE may improve current treatment options.

HEALTH ECONOMIC ASPECTS OF DEMENTIA PREVENTION

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Rationale: Given the present and expected future numbers of people with dementia worldwide, there is great interest in developing strategies that can influence these trends. Both cardiovascular risk factors and life style factors have in epidemiological studies been shown to be associated with dementia risk. In the multi-domain FINGER project, significantly positive effects on cognition and function were achieved. Thus there is a great hope that primary or secondary prevention programs could have important impacts on future numbers of people with dementia. However, we do not know their long-term effects or long-term cost-effectiveness.

Methods: A health economic simulation based on the results from FINGER will be presented. A comprehensive sensitivity analysis is included. The simulations will also compare prevention with simulations for the potential cost effectiveness for (still not existing) disease modifying treatments for Alzheimer´s Disease.

Results: The presentation will consider the number needed to treat (NNT) in a prevention program like FINGER and its related costs to avoid one case of dementia, as well as the incremental cost-effectiveness ratio with QALYs (quality adjusted life years) as the outcome.

Conclusions: In all simulations, prevention was cost effective. The magnitude of the results will be discussed.

Abstracts for scientific posters

Abstract number indicates the poster board number

P1

ASSOCIATION OF DIETARY CHOLINE AND PHOSPHATIDYLCHOLINE INTAKES WITH RISK OF INCIDENT DEMENTIA AND WITH COGNITIVE PERFORMANCE: THE KUOPIO ISCHAEMIC HEART DISEASE RISK FACTOR STUDY

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Rationale: Moderate egg intake has had a beneficial association with cognitive performance in some observational studies. As egg is a major dietary source of choline, especially phosphatidylcholine, we investigated the associations of choline and phosphatidylcholine intakes with incident dementia and cognitive performance in middle-aged and older men.
Methods: The study included 2497 dementia-free men aged 42-60 y in 1984-1989 at the baseline examinations of the prospective Kuopio Ischaemic Heart Disease Risk Factor Study. Dietary intakes were assessed with 4-day food recording. Data on five different cognitive performance tests at the 4-y re-examinations was available for a subgroup of 482 men. Dementia diagnoses wer e based on Finnish health registers. Cox regression and ANCOVA were used for the analyses.
Results: The mean±SD choline intake was 431±88 mg/d (18.3% from eggs), of which 188±63 mg/d was phosphatidylcholine (38.8% from eggs as the main source). During the mean 21.9-y follow-up, 337 men were diagnosed with dementia. Those in the highest (>222 mg/d) vs. the lowest (<144 mg/d) phosphatidylcholine intake quartile had 28% (95% CI: 1-48%; P-trend=0.02) lower multivariable-adjusted risk of incident dementia. Choline intake was not associated with the risk of incident dementia. However, both choline and phosphatidylcholine intakes were associated with better cognitive performance on tests of frontal and temporal lobe functioning. For example, higher intakes were associated with better performance in verbal fluency and memory functions.
Conclusions: Higher phosphatidylcholine intake was associated with a lower risk of incident dementia and with better cognitive performance in eastern Finnish men.

P2

MYBRAINCOACH: A PUBLIC HEALTH AWARENESS CAMPAIGN TO PROMOTE A BRAIN-HEALTHY LIFESTYLE

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Rationale: Preventing or delaying dementia is a public health priority, but requires rigorous definition of target groups and tailored strategies for prevention. We previously developed the 'LIfestyle for BRAin Health' (LIBRA) index that captures lifestyle-related dementia risk and flags individual room for improvement. An implementation project that uses this score in a public health campaign to raise awareness for dementia prevention has been launched in March 2018.

Methods: MyBraincoach is a public health campaign ('we are the medicine') targeting people aged 40-75 years in the Province of Limburg. An eHealth platform is constructed that will give people insight into their personal room of improvement and individual target behaviours using LIBRA. A baseline assessment of the public knowledge about brain and lifestyle has been carried out in ~600 people.

Results: Most people were unaware of a relation between lifestyle and dementia risk. Among a list of potential risk factors, cognitive and physically activity and healthy diet were identified most frequently, while vascular risk factors were named less often. 'Lack of knowledge' was the largest barrier for engaging in a brain-healthy lifestyle, and most people stated they would like to use an app to help them change their health behaviour.

Conclusions: There is a public need for more information and support to help people maintain a healthy brain and prevent or delay dementia onset. MyBraincoach is a unique project that raises public awareness and gives people insight into their own dementia risk profile and personal lifestyle advice that supports long-term brain health.

P3

CHARACTERIZATION OF TAU EXPRESSING P301S MOUSE MODEL FOR TAUOPATHY - LONGITUDINAL BRAIN STRUCTURAL AND METABOLIC PROFILE

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P301S (B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J) mouse is a widely used tauopathy model. Majority of the work described for the model focuses on the brain pathology after 6 months of age, when there has been reported more prominent tau pathology, neuronal cell loss and atrophy. As the early development of tauopathy, behavioral phenotype and both structural and metabolic profile of the brain in P301S (TG) were longitudinally compared to age-maatched wild type (WT) mice using anatomical imaging, 1H-spectroscopy, metabolic imaging (PET) together with behavioral assays. Wild-type (WT) and P301S mice were studied starting at age of 2 months and followed up until age of 8-10 months. Behavioral battery included motor assays and selected cognitive assays. For the brain structural analysis, we applied T2-MRI to evaluate whole brain, cortical, hippocampal, striatal and ventricle volumes over time between WT and TG mice. In addition, we performed 1H-MRS to examine metabolic profiles over time on corresponding time-points. Furthermore, PET imaging was applied to evaluate metabolic activity as well as in vivo inflammation. We report longitudinal characterization of P301S mouse line. Data indicates that P301S model has a small but clear brain structural and metabolic phenotype as evidenced by T2-MRI and 1H-MRS when compared to WT mice already from two months of age. P301S mice are also cognitively impaired in RAWM and CFC tests compared to corresponding wild type mice. Phenotyping with translational tools provides compelling readouts for drug development.

P4

INTRANASAL INSULIN ACTIVATES AKT2 SIGNALING PATHWAY IN THE MOUSE HIPPOCAMPUS

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The risk for Alzheimer's disease (AD) is increased by type 2 diabetes mellitus (T2DM). Post-mortem studies have revealed insulin resistance in the AD brain, while T2DM has been associated with brain atrophy in the regions strongly affected in AD. Furthermore, reduced glucose metabolism in the cortex and hippocampus as measured by fluorodeoxyglucose positron emission tomography (FDG-PET) is a key finding in AD. Thus, increasing brain insulin levels via intranasal insulin delivery has been suggested as a treatment for AD. A key player in insulin signaling is the Akt family of serine/threonine kinases, whose downstream signaling has b een associated with crucial physiological functions of the brain, such as promoting dendritic spine and synapse formation. Here, we investigated how intranasal insulin treatment modulates glucose metabolism in dif ferent brain areas of 14-month-old wild-type (WT) an d APPSwe/PS1dE9 (APP/PS1) mice u sing FDG-PET imaging, and how this treatment affects spatial learning and memory. We also wanted to assess hippocampal insulin signaling directly by measuring Akt1 and Akt2 phosphorylation in the hippocampus upon intranasal insulin treatment. We show that intranasal insulin treatment moderately increased glucose metabolism in the ventral brain, including the hippocampus. Further, intranasal insulin specifically activated hippocampal Akt2 and its downstream signaling more effectively in WT than in APP/PS1 mice. Intranasal insulin slightly impaired spatial memory in APP/PS1 mice. Our results suggest that intranasal insulin treatment increases glucose metabolism in the hippocampus via activating the Akt2 signaling pathway.

P5

OLDER EUROPEANS' REASONS FOR PARTICIPATING IN A MULTINATIONAL HEALTH PREVENTION TRIAL: A CROSS-COUNTRY COMPARISON USING MIXED METHODS (ACCEPT-HATICE)

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Rationale: ACCEPT-HATICE is a mixed-method sub-study of HATICE, a randomised controlled trial conducted in Finland, France, and the Netherlands to investigate the efficacy of an eHealth multimodal intervention in improving older adults' management of risk factors for cardiovascular disease and cognitive decline. ACCEPT-HATICE aimed to explore reasons for participating in HATICE, and to compare motivations among countries.

Methods: During the recruitment for HATICE, eligible individuals scheduled for screening were invited to complete an online questionnaire exploring reasons for participation with a pre-defined list of statements (response rate 79 %; N=341). Semi-structured interviews were performed within a sub-sample of respondents (N=46). Questionnaire data were analysed with ANOVA, Kruskal-Wallis, and chi-squared tests, and structured content analysis was applied to the interviews.

Results: Contributing to scientific progress (85 %), improving lifestyle (84 %), and receiving additional medical monitoring (79 %) were overall the most common reasons for participation. However, the level of importance given to each reason varied among countries. Based on the interviews, altruistic reasons were particularly relevant in France, whereas Finnish and Dutch participants emphasised the health benefits of lifestyle changes and the importance of regular check-ups to confirm good health or to detect health problems. Preventing functional dependence emerged as a common concern and underlying motive for participation.

Conclusions: Contributing to science, benefitting from lifestyle changes and medical attention, and preventing functional dependence motivated older adults to participate in a multinational eHealth prevention trial. These findings may facilitate the recruitment and design of future trials targeting older adults.

P6

INCREASED CORTICAL BETA POWER AND SPIKE-WAVE DISCHARGES IN MIDDLE-AGED APP/PS1 MICE

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Amyloid plaque forming transgenic mice display neuronal hyperexcitability, epilepsy and sudden deaths in early adulthood. However, it is unknown whether hyperexcitability persists until middle ages when memory impairment manifests. We recorded multichannel video-EEG, local field potentials and auditory evoked potentials in transgenic mice carrying mutated human APP and PS1 genes and wild-type littermates at 14-16 months as we have done earlier for 4-month-old mice. Further, we monitored acoustic startle responses in other APP/PS1 and wild-type mice from 3 to 11 months of age. Middle-aged APP/PS1 mice demonstrated increased cortical power at 8-110 Hz with an additional peak at 20-40 Hz not seen in young mice. They also displayed 15-fold increase in the occurrence of spike-wave discharges and augmented auditory evoked potentials compared to nontransgenic littermates. In contrast to evoked potentials, APP/PS1 mice showed normalization of acoustic startle responses with aging. Increased cortical beta-power and spike-wave discharges provide powerful new biomarkers to monitor progression of amyloid pathology in preclinical intervention studies.

P7

ADHERENCE OF OLDER ADULTS TO THE GUIDELINES FOR THE MANAGEMENT OF CARDIOVASCULAR DISEASE RISK: A EUROPEAN PERSPECTIVE

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Rationale: Dementia has been linked to modifiable cardiovascular risk-factors (CVRFs) not optimally controlled in older adults, providing opportunities for prevention. Evidence is lacking on how older adults can benefit from stricter management of CVRFs. We aimed to assess the adherence of older adults from different European countries to the guidelines for the management of cardiovascular disease risk.

Methods: Adherence to the recommendations for smoking, diet, physical-activity, overweight, hypertension, and diabetes was assessed in three European (Finland, France, the Netherlands) cohorts of older adults, based on the respective national guidelines. For hypertension and diabetes, treatment and treatment success rates were also calculated. Results were compared among the three countries.

Results: Generally, the Dutch cohort adhered less to lifestyle recommendations compared to Finnish and French. Although the Finnish cohort had the highest average BMI, the French cohort had the largest proportion of people eligible for a weight-reduction intervention (58.1%, $p<0.001$), due to stricter cut-offs. For hypertension, the Finnish cohort had a marginally higher treatment rate (90.4%, $p<0.001$) compared to both other countries, but the French had the highest treatment success rate (87.8%, $p<0.001$). The Dutch cohort had, instead, the best treatment success rate (95.8%, $p<0.001$) for diabetes.

Conclusions: Differences in adherence to the guidelines for the management of CVRFs across the three cohorts could mirror discrepancies in their recruitment and among the national guidelines, as well as cultural and healthcare differences. These finding could help identifying more effective strategies for the design of multidomain preventive intervention and public health programmes.

P8

BRAIN DISTRIBUTION OF L-TYPE AMINO ACID TRANSPORTER 1 (LAT1)-UTILIZING PRODRUGS

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L-Type amino acid transporter 1 (LAT1) is a transmembrane protein that carries neutral amino acids, but also drugs into the cells. It is highly expressed on the cell surfaces that require a constant amino acid supply, such as endothelial cells of blood-brain barrier, neurons and glial cells. In this study, cellular uptake of structurally diverse LAT1-utilizing neuroprotective prodrugs into mouse primary neurons, astrocytes and immortalized microglia (BV2) was explored. Furthermore, effects of Alzheimer's disease (AD; APdE9) on the cellular uptake of these prodrugs was studied. The LAT1-mediated cellular uptake of prodrugs and their parent drugs in each cell type was determined by liquid chromatography mass spectrometry. All prodrugs had 2-18-times higher cellular uptake in brain cells than their parent drugs. Moreover, some of the prodrugs released their parent drugs within the cells, indicating that these cells possess sufficient enzyme activity for prodrug bioconversion. Depending on the prodrug structure, selectivity between neuron-, astrocyte- and microglia- uptake was recognized. Interestingly, there was no significant difference in prodrugs' uptake into wild type astrocytes compared to transgenic AD-astrocytes. Therefore, these results show that cellular uptake can be significantly increased by LAT1-utilizing prodrugs within the brain. This can also be achieved in cells that are already predisposed to the pathological changes of AD. Furthermore, by careful prodrug design cell-selective targeting between neurons, astrocytes or microglia can be obtained. Thus, this prodrug approach has a great potential to improve targeted drug delivery and subsequently efficacy of neuroprotective drugs.

P9

INVOLVEMENT OF THE FRONTOTEMPORAL DEMENTIA GENE C9ORF72 IN PROTEASOME- AND AUTOPHAGY-MEDIATED PROTEIN DEGRADATION PATHWAYS

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Rationale: Hexanucleotide repeat expansion in C9orf72 gene is a major genetic contributor to frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Pathogenesis of FTD and ALS is suggested to involve impairment of protein degradation pathways, including ubiquitin-proteasome system and autophagy. The normal function of C9orf72 is only beginning to unravel, but interestingly, recent publications have suggested that C9orf72 isoform A is a negative regulator for autophagy.

Methods: We have utilized overexpression of C9orf72 isoforms A and B in N2a mouse neuroblastoma cells and mature mouse primary cortical neurons and siRNA-mediated knockdown of endogenous C9orf72 in HEK293 human embryonic kidney cells. To modulate the protein degradation pathways, we used lactacystin to inhibit the proteasome, serum starvation to induce autophagy, and bafilomycin A1 (BafA1) to block autophagosomal degradation.

Results and Conclusions: The levels of both C9orf72 isoforms increased after proteasomal inhibition in both of our neuronal models, suggesting that C9orf72 levels are regulated by proteasomal degradation. Induction of autophagy led to a decrease in the levels of both C9orf72 isoforms, but these were not restored by BafA1 treatment in N2a cells. BafA1 treatment in mouse primary cortical neurons decreased both C9orf72 isoform levels. Our findings suggest that C9orf72 proteins are not degraded by autophagy nor does their overexpression affect autophagy. In contrast, knockdown of C9orf72 in HEK293 cells led to decreased p62 levels, suggesting that the autophagic flux might be increased. Ongoing studies will provide further insights into the mechanistic role of C9orf72 proteins in the regulation of these protein degradation pathways.

P10

DIETARY INTERVENTION GOALS AT BASELINE IN RELATION TO COGNITIVE CHANGES DURING 2 YEARS: THE FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY (FINGER).

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Rationale: FINGER is a multi-center, randomized lifestyle intervention trial that showed beneficial effect on cognition with dietary guidance, exercise, cognitive training and management of risk factors. Here, we investigate the association between dietary intervention goals at baseline and cognitive function over 2 years.

Methods: Individuals aged 60-77 years were randomized to intervention (n=631) or control (n=629) group. A modified neuropsychological test battery and 3-day food records were executed annually. Goal of the dietary intervention was a diverse diet meeting dietary recommendations, defined by an adherence score with 9 distinct goals: saturated fat <10 E%, polyunsaturated 5-10 E%, fiber >3 g/MJ, sucrose <10 E%, protein 10-20 E%, alcohol <5 E%, fish 2 x week, vegetables >200 g/d, and fruit and berries >200 g/d. A mixed model regression adjusting for several potential confounders was applied.

Results: Total adherence score was not associated with cognitive function at baseline, but meeting the vegetable goal was. Higher baseline adherence score predicted more cognitive improvement in two years. Meeting vegetable, fruit and berries, or fiber intake goals at baseline also predicted more cognitive improvement. Alcohol goal was associated with worse baseline cognition and less improvement. In addition, baseline saturated fat intake predicted less improvement and polyunsaturated fat more improvement as continuous variables.

Conclusions: Fruit and vegetable consumption and fiber intake according to national recommendations are associated with better cognitive change. Saturated and polyunsaturated fat intakes may have a role in cognitive change, but intake levels optimal for brain-health remain unclear.

P11

USE OF HEALTH CARE SERVICES IN OLDER ADULTS PARTICIPATING IN FINGER MULTIDOMAIN INTERVENTION

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Rationale: Older age increases the prevalence of diseases that affect physical and cognitive functioning, and thus older adults are among the main users of health care services. However, with healthy lifestyle it may be possible to maintain good health and subsequently decrease the need for health care. This study investigates the use of health care among persons taking part in two-year lifestyle intervention.

Methods: The study involved 1260 older adults who participated in the FINGER randomized controlled trial. The 2-year intervention consisted of dietary counselling, physical exercise, cognitive training and monitoring of vascular risks. Logistic and negative binomial regression analysis were used to investigate the probability of doctor and nurse visits and inpatient hospital days in the intervention group compared to the controls.

Results: Logistic regression analyses, adjusted for sex, baseline age and health care visits during 12 months prior baseline, showed that after 2-year intervention persons in the intervention group were 30% less likely to report nurse visits within previous 24 months (OR 0.73, 95% CI 0.57-0.94). Also probability for visiting doctor in health care center within 24 months was significantly lower in the intervention group (OR 0.66, 95% CI 0.46-0.93). Negative binomial regression model adjusted for sex and baseline age showed that persons in the intervention group had lower probability for hospital inpatient days compared to the controls (IRR 0.79, 95% CI 0.63-0.99).

Conclusions: The preliminary analyses showed that a two-year multidomain lifestyle intervention may reduce the need of health care services.

P12

DELUSIONS AND AGITATION ARE RELATED TO AD PROGRESSION AND CAREGIVER DISTRESS ALSOVA FOLLOW-UP STUDY

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Rationale: Neuropsychiatric symptoms (NPS) are remark able but less investigated symptoms of Alzheimer's disease (AD). Family ca regivers face variety of demands while caring for a person with AD. The knowledge about the role of specific NPS in AD progression, prognosis and caregiver distress is limited. Our aims were to determine which baseline NPS predict AD progression, and which NPS with demographic factors are associated with family caregivers' psychological distress.
Methods: 236 persons with very mild or mild AD at baseline were annually followed up for five years in the ALSOVA study. Caregiver distress data was available for 226 caregivers, up to three years. The Neuropsychiatric Inventory (NPI) was used to assess NPS, the Clinical Dementia Rating Sum of Boxes (CDR-sb) as a measure of AD progression, and the General Health Questionnaire as a measure of caregiver distress. Data was analyzed with GEE and LMM models.
Results: The baseline NPS that best predicted AD progression during a five-year follow-up were delusions, agitation, and aberrant motor behavior. Delusions, agitation, and sleep disturbances were associated with family caregivers' psychological distress during a three-year follow-up. A marital relationship was associated with family caregiver distress. Mood-related symptoms, as depression, anxiety and irritability, were common but not related to AD progression or distress.
Conclusions: Persons with mild AD presenting delusions, agitation, and aberrant motor behavior at the time of diagnosis may have a more rapidly progressing disease. Delusions, agitation, and sl eep disturbances may cause di stress to t he family caregivers of persons with AD, especially if living together.

P13

LIFE-LONG PHYSICAL EXERCISE IS BENEFICIAL IN ALZHEIMER'S DISEASE

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Rationale: Aging is the highest risk factor for neurodegenerative diseases including Alzheimer's disease (AD): a devastating disorder characterised by cognitive impairment, abnormal accumulation of beta-amyloid deposits (Aβ) and neurofibrillary tangles, inflammation and sustained cellular stresses. Because of lack in medical treatments against age-related brain diseases including AD, changes in lifestyle could be a possible preventative approach. Physical exercise is known to be beneficial for brain health, but it is not yet fully understood how life-long exercise modulates AD progression. The aim of this study was to assess how life-long voluntary physical exercise affects the brain function behavioural phenotype of AD mice.

Methods: Transgenic 5xFAD mice modelling AD and their wildtype (WT) littermates were divided into sedentary and life-long exercise groups, in which the exercise paradigm was initiated at the age of weaning. Running distance and time were monitored on a weekly basis for the duration 8 months, during which the activity, memory, and cognition of the mice were assessed monthly by a battery of behavioural tests.

Results: This study demonstrated that while the running distance was not differ between WT and AD mice, the 5xFAD mice were impaired in nest building behaviour, locomotor activity, anxiety and memory. Importantly, long-term voluntary physical exercise reduced the impairment in nest building behaviour, altered locomotor activity and alleviated memory deficits of 5xFAD mice.

Conclusions: Taken together, these findings suggest that life-long physical exercise strongly modulates several behavioural phenotypes observed in AD mice. Supported by Biocenter Finland/Biocenter Kuopio

P14

AMYGDALA ALPHA-SYNUCLEIN PATHOLOGY IN THE POPULATION-BASED VANTAA 85+ STUDY

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Rationale: In addition to following well accepted theory of caudal to rostral progression, occasionally amygdala alpha-synuclein pathology has been observed to concentrate on amygdala. This amygdala-predominant category has been associated to Alzheimer's disease (AD) related pathology in disease-based clinicopathological studies. However, neither population- nor community-based studies have confirmed this. Furthermore, the knowledge of amygdala alpha-synuclein pathology of the eldest age group remain scarce. We investigated frequency of amygdala alpha-synuclein pathology and amygdala-predominant category of the very elderly individuals of Vantaa 85+ Study thus complementing the former work of alpha-synuclein pathology in this cohort.

Methods: Amygdala samples (N=304) of Vantaa 85+ Study were immunohistochemically stained with two alpha-synuclein antibody, clones syn42 and 5g4. Slides were semiquantitatively scored and compared with formerly analyzed alpha-synuclein and AD pathology from other brain regions.

Expected results: Amygdala alpha-synuclein pathology was hypothesized to appear mainly concomitant with alpha-synuclein pathology from other brain regions, though also amygdala-predominant cases were presumed to be found. Cases formerly categorized as non-classifiable were expected to fall to amygdala-predominant category. Amygdala-predominant category was suggested to associate with AD pathology.

Conclusions: Amygdala alpha-synuclein pathology was mainly concomitant with alpha-synuclein pathology from other brain regions. No significant difference between two antibodies were observed. From twelve amygdala-predominant cases, five were formerly categorized as non-classifiable, one limbic, one brainstem and five were negative. Amygdala-predominant category was small and heterogenous with no clear association to AD pathology and formerly determined so-called pure AD cases did not associate with amygdala alpha-synuclein pathology.

P15

L-TYPE AMINO ACID TRANSPORTER 1 UTILIZING PRODRUGS: PROMISING APPROACH TO TARGETED BRAIN DELIVERY OF CNS-ACTING DRUGS

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Rationale: The transporter-mediated prodrug approach is promising for improving brain uptake of CNS agents. To that end, the L-type amino acid transporter 1 (LAT1) is of high interest, exemplified by the antiparkinsonian drug L-Dopa and several prodrugs of CNS agents developed to utilize this transporter for brain delivery. However, there is a lack of knowledge of pharmacokinetics and intra-brain distribution of LAT1-utilizing prodrugs. The purpose of the study was to investigate pharmacokinetics of LAT1-utilizing prodrugs of the cyclooxygenase (COX) inhibitor ketoprofen with focus on blood-brain barrier transport and intra-brain distribution. The specific aim was to identify whether this approach enables selective delivery of the parent drug into the intracellular compartment of the brain parenchyma, where the target protein of ketoprofen, COX, and metabolizing enzymes responsible for the release of parent drug, are located.

Methods: The pharmacokinetic profile of unbound prodrug, released parent drug and ketoprofen itself in plasma, brain and liver after 25 μmol/kg i.p. bolus injection in mice were previously studied. The prodrug demonstrating successful brain delivery of ketoprofen with minimized liver exposure was selected for the current intra-brain distribution study using the brain slice method in mice. Transport to the brain parenchymal intracellular compartment was assessed by estimation of unbound intra-to-extracellular concentration ratio (Kp,uu,cell), with values above unity indicating active uptake into the cells. The mechanism of LAT1-mediated transport in brain slices was assessed using a recently developed selective LAT1 inhibitor. Moreover, LAT1 protein expression in brain slices was investigated using LC-MS based quantitative targeted proteomics approach.

Results: A LAT1-utilizing prodrug with aromatic amino acid promoiety conjugated to ketoprofen demonstrated 10-fold higher unbound brain to plasma ratio of the released ketoprofen (AUCu,brain/AUCu,plasma) than that after ketoprofen dosing. The liver exposure to released ketoprofen from this prodrug (AUCu,liver/AUCu,brain) was 5 times lower than after ketoprofen dosing. Intra-brain distribution study showed 16 times higher unbound volume of distribution for the prodrug (24.3 ± 2.1 mL×g brain-1), than that for ketoprofen (1.5 ± 0.13 mL×g brain-1) in mouse brain slices. The prodrug distributed into the cells (Kp,uu,cell 1.5 ± 0.63), while ketoprofen stayed in the extracellular fluid (Kp,uu,cell 0.22 ± 0.1). In contrast to pharmacokinetic study, ketoprofen release was not observed in brain slices. LAT1 expression in the brain slices was confirmed. In addition, LAT1 was involved in transport of the prodrug into the brain parenchyma, as Kp,uu,cell values decreased up to 1.05 ± 0.25 after incubation with the inhibitor.

Conclusions: The study provided important information for successful application of the LAT1-mediated prodrug approach for targeted delivery of CNS agents into the brain

parenchymal cells with minimization of systemic exposure. We demonstrated that the approach can improve the delivery of CNS agents with targets located in the intracellular compartment of the brain parenchyma.

P16

EXECUTIVE FUNCTION, VISUOCONSTRUCTION AND GLOBAL COGNITION ARE ASSOCIATED WITH ACTIVITIES OF DAILY LIVING IN ALZHEIMER'S DISEASE: ALSOVA FOLLOW-UP STUDY

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Rationale: Alzheimer's disease (AD) is characterized by progressive decline in cognition and activities of daily living (ADL). Recent research has indicated that some cognitive domains, particularly executive function, may be more strongly related to ADL than other domains. However, cognition-ADL relationships have been often studied cross-sectionally, in mild stage and with varying cognitive and ADL measures, restricting drawing of conclusions regarding the importance of different cognitive domains in ADL during different stages of AD. We aimed to study which cognitive domains were associated with instrumental activities of daily living (IADL) and basic activities of daily living (BADL) in a 5-year follow up of persons with AD.
Methods: We analysed data from 236 persons with very mild or mild AD at baseline as part of the ALSOVA study. Cognition was assessed using Consortium to Establish A Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) and ADL, consisting of IADL and BADL sub-scores, using Alzheimer's Disease Cooperative Study ADL (ADCS-ADL) questionnaire for care-givers. Linear mixed-effect models (LMMs) were used to analyse the 5-year follow-up data.
Results: Clock Drawing Test (CDT), Constructional Praxis and Mini-Mental State Examination (MMSE) were associated with BADL in the 5-year LMMs. The same measures, in addition to Verbal Fluency, Boston Naming Test (BNT), Word List Recall and Constructional Praxis Recall, were associated with IADL and A DCS-ADL total score.
Conclusions: Executive function, visuoconstruction and global cognition measures were associated with both BADL and IADL. This information can be utilized in AD assessment and monitoring.

P17

THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA LONGITUDINAL COHORT STUDY (EPAD LCS)

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Rationale: The European Prevention of Alzheimer's Dementia (EPAD) project is funded by the Innovative Medicines Initiative. It has been established to overcome the major hurdles hampering drug development for secondary prevention of Alzheimer's dementia, by conducting the EPAD Longitudinal Cohort Study (LCS), in alignment with the Bayesian adaptive designed EPAD Proof of Concept (PoC) trial.

Methods: EPAD LCS is an ongoing prospective, perpetual, multicentre, pan-European longitudinal cohort study. Participants are recruited mainly from existing Parent Cohorts (PC) across Europe, but also from clinical settings without a PC, to form a 'probability-spectrum' population covering the entire continuum of anticipated probability for Alzheimer's dementia development. Two main objectives of EPAD LCS are to provide a readiness cohort for the EPAD PoC trial, and to generate a large comprehensive dataset for developing and continuously improving disease models for AD in in dividuals without dementia.

Results: EPAD LCS is conducted in a network of highly selected, expert sites chosen on the basis of strictly applied criteria to ensure the highest possible data quality, successful recruitment and adherence to the EPAD principles. Recruitment for EPAD LCS is currently ongoing, and continuous updates on the status of the cohort are shown on the EPAD website at *http://ep-ad.org/*. As of April 2018 fourteen (14) Trial Delivery Centres in 7 countries have recruited 614 research participants.

Conclusions: The multi-national approach and acad emia-industry collaborations are essential for advancing knowledge on the entire spectrum of AD, and for finding effective therapies to prevent the onset of dementia.

P18

CARDIORESPIRATORY FITNESS AND COGNITIVE FUNCTIONS: LONGITUDINAL ASSOCIATIONS IN THE FINGER STUDY

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Rationale: Previous studies have fo und positive associations between cardiorespiratory (CRF) and cognitive functions in elderly people but data are inconsistent. Our aim was to study the longitudinal associations of CRF with overall cognitive function as well as with the domains for executive functioning, processing speed, and memory in elderly people at risk for cognitive decline.

Methods: Participants (n=421), mean age 69 (SD 4.6), were a su b-sample of The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). To be eligible, individuals were required to be 60-77 years old with a presence of some modifiable vascular risk factors and cognitive performance at the mean level or slightly lower than expected for age according to Finnish population norms. CRF was assessed as peak oxygen uptake (VO2peak, L/min) measured in a maximal exercise test on cycle ergometer at baseline and at 24 months. Cognitive function was assessed using an extended version of the Neuropsychological Test Battery (NTB) at baseline and at 24 months. NTB data were standardized to Z scores, and analyzed with the linear mixed model.

Results: Over two years, VO2peak was associated with NTB total score (β=0.12, p=0.01) as well as with the cognitive domains for executive functioning (β=0.16, p=0.01) and processing speed (β=0.25, $p < 0.001$), but not with memory (β=0.11, p=0.12). Conc lusions Over two years follow-up, high CRF associated with better overall cognition as well as with the domains for executive functioning and processing speed in at-risk elderly people.

P19

SERUM AND CEREBRO SPINAL FLUID NEUROFILAMENT LIGHT IN COGNITIVELY HEALTHY SUBJECTS

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Rationale: Neurofilament proteins are prospective biomarkers of axonal damage. Previously, accurate quantification of neurofilament proteins has been limited to using cerebrospinal fluid (CSF) due to low neurofilament concentrations in other sources. With modern ultra-sensitive assays, neurofilament light (NFl) can now be accurately quantified from sources outside the central nervous system. We examined the correlations between Alzheimer's disease CSF biomarkers and concentrations of CSF and serum NFl in cognitively healthy subjects. We will also examine the effects of demographic variables on the concentrations of NFl in healthy subjects.

Methods: Serum NFl was quantified from 83 cognitively healthy patients with osteoarthritis using automated enzyme linked immunosorbent assay (Quanterix SIMOA, Lexington, MA, USA). Quantification for CSF NFl will utilize the same methodology. The CSF samples were drawn before the delivery of a spinal anesthetic in arthroplasty surgery. Serum samples were obtained post-surgery. Patient's cognitive status was evaluated with mini-mental-state examination or with a phone questionnaire.

Results: Our initial findings display a positive correlation between serum NFl and both CSF total and phosphorylated TAU. Serum NFl had no significant correlation with CSF beta-amyloid 1-42. Furthermore, serum NFl correlates positively with age, but is unaffected by sex.

Conclusions: Our findings suggest that serum NFl might reflect the CSF biomarkers of neurodenegeration even in cognitively healthy subjects. We also conclude that age can have a significant impact on NFl concentrations in serum.

P20

THE ROLE OF SEPT5 IN THE APP PROCESSING IN SH-SY5Y-APP751 NEUROBLASTOMA CELLS

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Septins (SEPT) have been proposed as potential candidates involved in the regulation of synaptic function in neurodegenerative diseases, such as Alzheimer's disease (AD). These proteins are implicated in several cellular processes, including formation, growth and stability of axons and dendrites, synaptic plasticity, and vesicular trafficking. We have previously shown a transcript variant imbalance for SEPT8 in human temporal cortex in relation to AD-related neurofibrillary pathology. Furthermore, the SEPT8 transcript variant imbalance correlated with β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) enzymatic activity. Moreover, SEPT8 potentially serves as a sorting protein for BACE1 subsequently altering APP processing and Aβ production. Our phosphoproteomic analysis of human AD brain samples revealed that SEPT5, a direct interaction partner of SEPT8, has phosphorylation changes in functionally relevant amino acids at early stages of AD-related neurofibrillary pathology. To further, characterize the potential role of SEPT5 in AD, human SH-SY5Y neuroblastoma cells overexpressing the APP751 isoform were transfected with a control plasmid, human SEPT5 wild-type or SEPT5 phosphomutants. Immature and mature APP were quantified by Western blotting assay from the total protein lysates obtained from cells. Aβ40 and Aβ42 levels were quantified by ELISA from the cell culture medium. Our results show that overexpression SEPT5 did not significantly alter APP processing and Aβ generation.

P21

DOES SEX MODERATE THE EFFECT OF AGE ON VERBAL EPISODIC MEMORY? A POPULATION-BASED STUDY OF 1777 INDIVIDUALS IN THEIR 70'S

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Rationale: Verbal episodic memory (EM) is affected early during the development of Alzheimer's disease. Moreover, older individuals and men have poorer verbal EM, but it is less clear if the age-verbal EM association differs by sex. We investigated the independent effects of sex, age, education and depressive symptoms and the interactive effect between age and sex on verbal EM in a population-based study of older adults using a word list learning test.

Methods: The participants were same-sex twin pairs born in 1938 - 1944 from the older Finnish Twin Cohort study (N = 1,777, age range 71 - 78). In 2013 - 2017, cross-sectional assessment of cognition was performed using modified Telephone Interview of Cognitive Status which includes the immediate and delayed free recall of a 10-word list. Depressive symptoms were assessed with CES-D. Linear regression models were used to examine the effects of independent variables on the word list recall score (total number of words in immediate and delayed recall, range 0 - 20).

Results: On average, women performed better than men. Education was positively related to EM and age and depressive symptoms were negatively related to EM. The effect of age on EM was stronger in women (N=882, B = -0.48, 95% CI -0.65, -0.32) compared to men (N=895, B = -0.23, 95% CI -0.35, -0.11), P for interaction = 0.013. Depressive symptoms did not affect this relationship.

Conclusions: Women had on average better verbal EM performance than men, but the difference became less evident with increasing age.

P22

PREVALENCE OF FRAILTY AMONG OLDER PEOPLE AT INCREASED RISK OF COGNITIVE IMPAIRMENT

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Rationale: Frailty syndrome is a common health problem among older people and it increases the risk of falls, hospitalization, disability and death. Frailty has multifactorial etiology and its prevalence varies greatly depending on the tools used and populations studied. The aim of this study is to investigate the prevalence of frailty syndrome among older people with increased risk of cognitive impairment.

Methods: This study reports baseline data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Frailty syndrome was defined with modified Fried's phenotype, which is based on following five criteria: weight loss, exhaustion, weakness, slowness and low physical activity. Participants were classified as frail if they had three or more of the listed criteria. Persons with one to two criteria were classified as pre-frail. Associations between frailty and population characteristics were investigated using T-test and chi-square test.

Results: Preliminary results showed that in the relatively healthy FINGER population (n=1135, mean age 69,3 years, SD 4,7) the prevalence of frailty and pre-frailty was 0,8% and 27,3%, respectively. There were no differences between men and women (p=0,24). Being frail or pre-frail was associated with poor self-rated health (p<0,001). Frail and pre-frail persons also had more chronic diseases compared with robust (p<0,001). In addition, frail and pre-frail persons had more often difficulties in activities of daily living (p<0,001).

Conclusions: Frailty was relatively rare in the FINGER population, but almost third of the population was pre-frail. Being pre-frail or frail was associated with poorer health and physical functioning.

P23

ALZHEIMER'S DISEASE AND SHIFT WORK INTOLERANCE SHARE GENETIC RISK VARIANT NEAR MELATONIN RECEPTOR 1A GENE

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Rationale: Disruption of the circadian rhythms is a well-known consequence of shift work and a frequent preclinical and clinical manifestation of Alzheimer's disease. In a recent study, we demonstrated association of the variant rs12506228 near melatonin receptor 1A gene (MTNR1A) with shift work intolerance (Sulkava et al. Sleep 2016, PMID 28364478). Here, we tested association of the same variant with Alzheimer's disease.

Methods: We genotyped the variant in two Finnish population-based cohorts of very elderly individuals, Vantaa 85+ and Kuopio 75+ (n~350 and 490), and in a younger Finnish case-control sample (n~1300). Vantaa 85+ included post-mortem neuropathological examination for half of the cohort. We studied also the effects of RNAi-mediated silencing or overexpression of MTNR1A on amyloid precursor protein (APP) processing in vitro.

Results: The risk variant of intolerance to shift work was associated with clinical Alzheimer's disease in Vantaa 85+ ($P < .0001$, OR=2.1) and in Kuopio 75+ ($P<0.05$, OR=1.5) but not in the younger case-control sample. The risk variant also showed association with higher amounts of neurofibrillary tangles and amyloid plaques ($P<0.005$). In silico, the risk variant was associated with lower level of MTNR1A expression in the brain according to publicly available eGWAS Mayo data. In vitro, silencing of MTNR1A decreased and over expression of MTNR1A increased amyloidogenic processing of APP.

Conclusion: We suggest the MTNR1A variant as a shared genetic risk factor for shift work intolerance and Alzheimer's disease among the very elderly. The association with AD is likely mediated by differences in MTNR1A expression modulating APP metabolism (Sulkava et al, Sleep in press).

P24

HIPPOCAMPAL SCLEROSIS IN THE OLDEST OLD: A FINNISH POPULATION-BASED STUDY

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Rationale: There are only few population-based studies that have systemically investigated the prevalence of hippocampal sclerosis (HS) in the very old. The frequency of unilateral vs. bilateral HS has been rarely studied.

Objective: We in vestigated the prevalence and laterality of HS and its association with other neurodegenerative and vascular pathologies in a population-based sample of very elderly. Furthermore, the concomitant presence of immunoreactivity for TDP-43, p62 and HPtau was studied.

Methods: The population-based Vantaa 85+ study includes all inhabitants of the city of Vantaa, who were > 85 years in 1991 (n= 601). Neu ropathological assessment was possible in 302 subjects. Severity of neuronal loss of CA sectors and subiculum was determined bilaterally by HE- staining. Immunohistochemistry performed using antibodies for TDP-43, p62 and HPtau.

Results: Neuronal loss and pathological changes in the hippocampus sector CA1 and subiculum were observed in 47 of the 302 individuals (16%), and 51% of these changes were bilateral. HS without comorbid neurodegenerative pathology was found in 1/47 subjects with HS (2%). Dementia ($p < 0.001$) and TDP-43 immunopositivity of the granular cell layer of the dentate fascia ($p<0.001$) were strongly associated with HS. The CERAD score, immunopositivity for HPtau and p62 in the granular cell layer of the fascia dentate were also associated.

Conclusion: HS is prevalent (16%) in the oldest old population, but HS without any comorbid neurodegenerative pathology is rare. The high frequency of unilateral HS (49 %) implied that bilateral sampling of hippocampi should be routine practice in neuropathological examination.

P25

CHARACTERIZATION OF EPILEPTIC SPIKING ASSOCIATED WITH BRAIN AMYLOIDOSIS IN APP/PS1 MICE AS NEW READOUTS IN PRECLINICAL TREATMENT TRIALS

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Rationale: All most common lines of amyloid precursor protein transgenic mice (TG), the primary model of Alzheimer (AD)-related brain amyloidosis, display some form of epileptic activity, including generalized seizures. However, the exact seizure focus awaits to be identified. In addition, a number of various discharges of short duration have been used as surrogate markers for their epilepsy in anti-epileptic treatment trials, but so far, these have been poorly characterized and highly variable between studies. We aimed at characterizing these short discharges in AD TG mice with well-documented seizure occurrence.

Methods: We implanted TG and WT mice with multiple chronic electrodes in cortical areas and hippocampus to record local field potentials. Two 3-h video-EEG recordings were conducted at the age of 5-6 months.

Results: We identified four subtypes of high-voltage single spike, one spike-wave complex, and a new type of discharge complex ("giant spike") that spreads to all recordings channels. These giant spikes were detected only during sleep and only in TG mice.

Conclusions: Our identified short-duration discharge patterns can be used as surrogate markers to per se rare spontaneous seizures in TG mice to help development optimal treatments for Alzheimer-related epilepsy.

P26

POTENTIAL SYNAPTIC DYSFUNCTION IN FRONTOTEMPORAL DEMENTIA

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Rationale: Frontotemporal dementia (FTD) is the second most common progressive neurodegenerative disease in individuals under 65 years. The most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS) is a hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (C9orf72) gene, suggesting that FTD and ALS pathogenesis are interlinked. We are interested in how the C9orf72 hexanucleotide repeat expansion influences dendritic spine morphology and synaptic composition and function. Over 90% of excitatory synapses are located in dendritic spines, which are small, dynamic, actin-rich morphological specializations that protrude on dendrites. Changes in dendritic spine morphology, i.e. structural synaptic plasticity, can be associated with strengthening or weakening of synaptic efficacy and function, as well as learning and memory.

Methods: The pathological C9orf72 hexanucleotide repeat expansions were overexpressed in mouse embryonic hippocampal neurons. Morphological changes in dendritic spines were analyzed by super-resolution confocal microscopy and NeuronStudio software. The potential effects of the repeat expansion on biochemical composition of synapses are assessed in synaptosomal extracts from the neurons. We also will utilize mouse brain samples and patient-derived induced pluripotent stem cells in our investigations.

Results and Conclusion: Our preliminary data upon overexpression of the pathological expanded C9orf72 hexanucleotide repeats in mouse primary hippocampal neurons and subsequent dendritic spine analysis show significant changes in the spine morphology and density. Our studies investigating the effects of C9orf72 hexanucleotide repeat expansion on synaptic function and dendritic spine modulation will provide important novel insights into the molecular pathogenic mechanisms underlying FTD and ALS.

P27

THE ROLE OF A SEGMENTAL COPY NUMBER LOSS OF THE SFMBT1 IN ALZHEIMER'S DISEASE-RELATED NEUROPATHOLOGY IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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Rationale: Idiopathic normal pressure hydrocephalus (iNPH) is a progressive neurodegenerative disease with unknown origin often manifesting with gait difficulties, incontinence, and cognitive impairment together with ventriculomegaly. Comorbid Alzheimer's disease-related pathology is frequently detected in iNPH patients. Recently, the copy number loss in SFMBT1 was found as a potential risk gene in iNPH. We aimed to determine the role of the copy number loss in SFMBT1 in the accumulation of beta-amyloid (Aβ) and hyperphosphorylated tau-protein (HPtau) among Finnish iNPH patients.

Methods: Overall 365 shunt-operated patients (n=37 carriers and n=328 non-carriers) with available cortical biopsies were evaluated from Kuopio NPH registry. Neuropathologist analysed the presence Aβ, HPtau and, in a subset of patients, the p62 protein. The presence of the genetic variant was detected by qPCR. Fisher's exact test was used to analyze the statistical difference ($p<0.05$) between groups.

Results: The copy number loss in the intron 2 of the SFMBT1 did not associate with the occurrence of Aβ ($p=0.86$), HPtau ($p=1.0$) or both ($p=0.79$). In addition, there was no significant differences between the ApoE ε4 allele or the accumulation of p62 between the copy number loss carriers and non-carriers.

Conclusions: This is the first study where the role of the copy number loss in SFMBT1 in the occurrence of Alzheimer's disease-related pathology was studied. Our results further validate the role of the copy number loss in SFMBT1 in iNPH and not in other common neurodegenerative diseases.

P28

ASTROCYTE PHENOTYPE AND FUNCTION ALTERATIONS IN AGING AND ALZHEIMER'S DISEASE

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Rationale: Astrocytes play a central role in maintaining central nervous system homeostasis. Recently it was reported that two types of astrocytes exist: the A1 astrocytes, induced by neuroinflammation, and A2 astrocytes, induced by acute brain injury. Little is known about how A1/A2 markers, astrocytic mitochondrial metabolism, or phagocytosis ability are affected during aging or neurodegeneration. Here we study astrocyte functions during aging and Alzheimer's disease (AD).
Methods: Primary astrocytes harvested from young (neonatal) and aged (5- and 11-month-old) wildtype and 5xFAD mouse brains were subjected to phenotypic characterization by RT-qPCR. Phagocytic ability was quantified by fluorescence imaging following pHrodo" Green Zymosan Bioparticles" Conjugates. Astrocytic mitochondrial functions were assessed by Agilent Seahorse XF technology, measurement of ATP levels by the ATPlite Luminescence Assay System, and by loading mitochondria with Rho123 dye and measuring the responses to the ATP and FCCP with live cell imaging.
Results: Our data demonstrate that aging is associated with an increase in A1 astrocyte markers and a reduction in A2 markers in WT mice. In contrast, A1 markers are reduced in astrocytes from 11-month-old 5xFAD mice. The cell's phagocytic ability is impaired in aged astrocytes and associated with decreased expression of the phagocytosis markers Mertk and Abca1. When compared to WT astrocytes, the aged 5xFAD astrocytes seem to display altered mitochondrial function and increased ATP production.
Conclusions: These results highlight alterations in astrocyte phenotypes and functions during aging and AD. Our further studies aim at understanding how impaired astrocyte functions impact brain health during aging and neurodegeneration.

P29

QUALITY OF LIFE IN RELATION TO NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER´S DISEASE: 5-YEAR PROSPECTIVE ALSOVA COHORT STUDY

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Rationale: To examine the association between neuropsychiatric symptoms (NPS) with self- and caregiver-rated Quality of Life (QoL) for patients with Alzheimer´s disease (AD) during a five-year follow-up.

Methods: The ALSOVA 5-year follow-up study included, at baseline, 236 patients with either very mild (Clinical Dementia Rating Scale (CDR) 0.5), or mild (CDR 1) AD, together with their caregivers from three Finnish hospital districts. QoL was evaluated using patient selfreported, and caregiver-rated, Quality of Life in Alzheimer´s disease (QoL-AD) scores. NPS were assessed using the Neuropsychiatric Inventory (NPI), AD severity was evaluated using the CDR, with cognition tested by the Mini-Mental State Examination (MMSE). The performance of daily activities were assessed using the Alzheimer´s Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL).

Results: Over the five-year follow-up period, patient self-reported QoL-AD scores did not change significantly (p=0.245), despi te increases in their NPS. However, caregiver-rated patient QoL-AD scores declined significantly (pd0.001), as total NPI scores increased during follow-up. No NPS at baseline, and only apathy at follow-up, correlated significantly (p=0.007) with patient self-rated QoL-AD scores. Caregiver-rated patient QoL-AD scores correlated significantly with most NPS, es pecially (pd0.001) apath y, agitation, anxiety, irritability, depression and delusions at baseline, and delusions, hallucinations, apathy, appetite disturbances and anxiety during follow-up.

Conclusions: Patient rated QoL-AD scores are an unreliable tool with which to evaluate the success of therapy for NPS. Instead, caregiver-rated scores for patients correlated well with NPI scores, and health care professionals in the clinic should preferentially use these.

P30

TRAJECTORIES FOR DIFFERENT COGNITIVE DOMAINS IN RELATION TO FUNCTIONAL DECLINE IN THE FINGER TRIAL

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Rationale: Cognitive and functional changes are essential outcomes in dementia prevention trials, but their relationship is complex and unclear. We conducted post-hoc analyses of changes in different cognitive domains in relation to functional decline during the Finnish Geriatric Intervention to Prevent Cognitive Impairment (FINGER) trial.

Methods: The modified Neuropsychological Test Battery was used to assess cognition at baseline, 1- and 2-year visits. Cognitive outcomes were total, memory, executive functioning, and processing speed scores. We measured functional decline using the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) questionnaire at baseline and 2-year visits (N=1045). We built mixed models for the cognitive outcomes using randomization group, time, ADL-decline, and the interactions of time with group and ADL-decline as factors.

Results: 324 (31%) of participants had ADL decline during the trial, and 721 (69%) were stable or improved. Participants with ADL-decline were slightly older and less educated. In the mixed model, baseline scores for ADL-decliners were lower for memory (-0,12; p=0,005), processing speed (-0,14; p=0,03) and total cognitive score (-0,10; p=0,008), and the annual improvement was lower for executive function (-0,04/year; p<0,001) and total cognitive score (-0,02/year ; p=0,03). Considering the effects of site, age and education, baseline difference for memory and annual change for executive function remained significant.

Conclusions: ADL-decliners had lower baseline memory than non-decliners, but there was no difference in improvement during the trial. For executive function, there were no baseline difference, but ADL-decliners did not improve their scores as much as non-decliners.

P31

THE ROLE OF METHYL-C PG-BINDING PROTEIN 2 PHOSPHORYLATION CHANGES IN ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

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Rationale: Synaptic dysfunction is one of the earliest correlates of the cognitive decline in Alzheimer's disease (AD). As an epigenetic modulator, Methyl-CpG-binding protein 2 (MeCP2) regulates the expression of several genes involved in structural and functional synaptic plasticity. Recently, it has been suggested that MeCP2 deficiency may alter microglial gene expression and play a role in microglial-mediated neurotoxicity.

Methods: Phosphoproteomics data was obtained from human post-mortem brain samples. Preliminary experiments were conducted, overexpressing MeCP2 in BV2 mouse microglial cells and inducing inflammation using lipopolysaccharide (LPS) and interferon-γ (IFNγ). Recently, S80 and S423 phosphorylation site-mutants of MeCP2 were generated. An in vitro co-culture model of neurons and microglia will be used to analyse synaptic structural plasticity.

Results: Phosphoproteomics data revealed a significant decrease in MeCP2 S423 phosphorylation during early stages of AD. Upon induced inflammation in BV2 cells, overexpression of MeCP2 increased the levels and expression of pro-inflammatory cytokines IL-6 and TNF± and decreased the expression of anti-inflammatory HMOX1. LPS/IFNγ-induced activation also led to MeCP2 stabilisation and increased expression of a major glutamine transporter SNAT1. The role of phosphorylation changes will be addressed expressing the phosphorylation site-mutants of MeCP2 in microglial cells.

Conclusions: Our preliminary findings suggest an involvement of MeCP2 in the early stages of AD-related neurofibrillary pathology and a role for MeCP2 in the regulation of the inflammatory response of microglial cells. Therefore, further characterization of MeCP2 phosphorylation changes in microglial cells and their impact on synaptic plasticity may provide new insights into the early stages of AD pathophysiology.

P32

MODELING C9ORF72 HEXANUCLEOTIDE REPEAT EXPANSION-RELATED FTD/ALS PATHOLOGICAL HALLMARKS IN CELLS

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Rationale: Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are two devastating neurodegenerative diseases for which there are no effective disease-modifying treatments. The hitherto most common known genetic cause of both FTD and ALS is a heterozygous hexanucleotide repeat expansion in the non-coding region of the C9orf72 gene. Modeling the pathological hallmarks of C9orf72 repeat expansion-associated FTD and ALS under controlled conditions and in different cell types is essential to reveal driving factors that lead to cellular alterations and finally neurodegeneration. Here, we aimed to establish in vitro neuronal- and microglial-like cell systems modeling the key pathological features of C9orf72 repeat expansion.

Methods: Neuronal N2a and microglial BV-2 cells were transfected with plasmids expected to induce C9orf72 repeat expansion-related pathological hallmarks of FTD and ALS. Fluorescence in situ hybridization, immunocytochemistry, fluorescence microscopy, and Western Blotting were utilized to confirm the presence of these hallmarks in our models. Viability and functionality of N2a and BV-2 cells harboring the pathological hallmarks at different time points after transfection will be assessed.

Results: Both N2a and BV-2 cells show presence of C9orf72 repeat expansion-related pathological hallmarks. Preliminary data regarding cell viability and functionality will be presented.

Conclusions: We were able to establish two different cell models mimicking central nervous system-resident cell types, which show pathological hallmarks of C9orf72 repeat expansion-associated FTD and ALS under controlled conditions. These models will serve as platforms to identify factors accompanying the pathological hallmarks and underlying neurodegeneration.

P33

EFFECT OF BERRIES ON COGNITIVE CHANGE DURING A 2-YEAR MULTI-DOMAIN LIFESTYLE INTERVENTION: THE FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY (FINGER)

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Rationale: Dietary components such as berries are part of the recommended Nordic diet, and are considered having health-enhancing characteristics. A randomized multi-center and multi-domain lifestyle intervention trial FINGER has shown benefits on cognition with dietary guidance, exercise, cognitive training and vascular risk management. Here, we investigate the association between berry intake at baseline and cognitive function over 2 years.

Methods: Individuals aged 60-77 years were randomly assigned in a 1:1 ratio to intervention (n=631, nutritional guidance, exercise, cognitive training, and management of metabolic and vascular risk factors) or con trol group (n=629, general h ealth advice). A modified neuropsychological test battery and 3-day food records were administered annually. Nutritional guidance was based on dietary recommendations including various nutritional components of the recommended diet such as berries. Mixed effects regression models adjusting for several potential confounders were applied.

Results: Higher berry consumption at baseline compared with no berry consumption at all was associated with more improvement in different cognitive domains: overall cognition 0.051, $p<0.001$; executive functioning 0.049, $p=0.003$; memory 0.057, $p=0.007$; and processing speed 0.044, $p=0.012$ over two years.

Conclusions: Berries are an important component of the Nordic diet, and higher consumption of berries seems to have a beneficial impact on cognitive functioning. High amount of flavonoids in berries might be behind this association, e.g. by influencing cerebrovascular blood flow and synaptic plasticity of the brain.

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P34

ASSOCIATIONS OF CAIDE DEMENTIA RISK SCORE WITH INFLAMMATION AND METABOLIC BLOOD BIOMARKERS IN THE FINGER STUDY PARTICIPANTS

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Rationale: The Cardiovascular Risk Factors, Aging, and Incidence of Dementia(CAIDE) Risk Score is a validated tool for estimating 20-year dementia risk at midlife based on age, sex, education, hypertension, obesity, hypercholesterolemia and physical inactivity. CAIDE Dementia Risk Score has been previously associated with structural brain changes and cognition in different populations. This study investigated associations of CAIDE Dementia Risk Score with inflammation and metabolic blood biomarkers in the Finnish Geriatric Intervention Study to prevent Cognitive Impairment and Disability (FINGER) participants.

Methods: Participants of the FINGER study were 1260 at -risk elderly, aged 60 -77years, without dementia or substantial cognitive impairment. At FINGER baseline, CAIDE Dementia Risk Score; assessments for 42 inflammation and metabolic blood biomarkers (cytokines, chemokines, growth factors and metabolic modulators) using the Bio-Plex 200 system; serum C-reactive protein (CRP) and homeostatic model assessment for insulin resistance (HOMA-IR) were available for 718 participants. Linear regressions were used to assess the cross-sectional associations between CAIDE Dementia Risk Score and inflammation and metabolic blood biomarkers at FINGER baseline using STATA software (version 12).

Results: Higher CAIDE Dementia Risk Score at FINGER baseline was associated with higher c-peptide ($p<0.001$), lower ghrelin ($p=0.019$), higher insulin ($p<0.001$), higher leptin ($p<0.001$), higher plasminogen activator inhibitor-1 ($p=0.006$), lower adiponectin ($p=0.048$), higher CRP ($p=0.003$) and higher HOMA-IR ($p<0.001$) after correcting for false discovery rate.

Conclusions: Preliminary results show that in this at-risk older population, CAIDE score was associated with metabolic biomarkers but not with markers of inflammation other than CRP.

P35

ACTIVE AGING AND COGNITION IN A 75-YEAR-OLD POPULATION

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Rationale: Active ageing is a globally promoted concept, and recently a scale was developed to quantify it on an individual level (University of Jyvaskyla Active Aging Scale, UJACAS; indicates older people's striving for well-being). Since activity participation can increase cognitive functioning and lower the risk of developing dementia, the aim of the study was to explore if UJACAS' total score or sub-scores (goals, ability, autonomy and activity) are associated with cognition.

Methods: The data come from the AGNES study, which is a population-based study of older adults living in the area of Jyväskylä, Finland. This study uses a sample of 211 women and men aged 75 years who were measured for UJACAS (range 0-272; higher score indicates higher activity) and Mini-Mental State Examination (MMSE). MMSE was classified as 1) high (score 29-30), 2) medium (score 25-28) and 3) low (score d24). General linear model was used for unadjusted and adjusted (physical functioning, education and depression adjusted) analyses.

Results: UJACAS score was higher among persons with a high MMSE as compared to persons with a medium ($p=0.017$) or a low ($p<0.001$) MMSE. Likewise, high scores in goals ($p=0.031$), ability ($p=0.012$), autonomy ($p=0.016$) and activity ($p=0.016$) were associated with high MMSE. However, after adjustment, UJACAS total score or any of the sub-scores were no longer associated with MMSE ($p>0.05$ for all).

Conclusions: Possibilities for successful active aging are not determined by cognition.

P36

DEPRESSIVE SYMPTOMS AND COGNITION IN THE FINGER TRIAL

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Rationale: Depression is associated with cognition, and both have been related to lifestyle factors. In the Finnish Geriatric Intervention Trial to Prevent Cognitive Impairment and Disability (FINGER), we conducted: 1) pre-specified analyses of intervention effects on change in depressive symptoms; and 2) post-hoc analyses of associations between depressive symptoms and cognition during the trial.

Methods: The 2-year multidomain lifestyle FINGER trial included 1260 elderly people at risk for cognitive decline. Individuals with dementia, major depression, or other conditions preventing cooperation or safe engagement in intervention were excluded. Primary outcome was change in overall cognition measured with a modified Neuropsychological Test Battery. Secondary outcomes included memory, executive functioning, psychomotor speed, and depressive symptoms evaluated with Zung scale at baseline, 1- and 2-year visits. Statistical methods included mixed effects regression and structural equation modeling.

Results: At baseline, people with more pronounced depressive symptoms had poorer cognition. However, only 3% of participants had Zung score higher than 50, suggesting possible clinical depression. Change in Zung score over time was not significantly different between the intervention and control groups. Preliminary results suggested an inverse association between depressive symptoms and change in executive functioning, but not in other cognitive domains, during the trial.

Conclusions: In individuals at risk for cognitive decline but without major depression at baseline, depressive symptoms seemed to have some effect on change in executive functioning during a 2-year multidomain lifestyle intervention.

P37

PREDICTORS OF PROGRESSION TO DEMENTIA AMONG MEMORY CLINIC PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND NORMAL CSF ²-AMYLOID

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Rationale: Individuals with mild cognitive impairment (MCI) and suspected non-amyloid pathology (SNAP), or normal cerebrospinal fluid (CSF) biomarkers are increasing groups of memory clinic patients. We investigated predictors of dementia in these groups.

Methods: 536 patients from Karolinska University Hospital memory clinic with CSF and clinical data were i ncluded. Follow-up was av ailable for 317 patients. MCI-SNAP was defined as abnormal CSF total tau (t-tau), or phosphorylated tau (p-tau), or both (N=132). Cox proportional hazards models with age as time scale and adjusted for sex and education were used to investigate potential predictors of progression to dementia.

Results: MCI-SNAP had higher risk of dementia compared to MCI-normal CSF (HR 2.2, 95% CI 1.5-3.3). MCI-SNAP patients were also significantly older at the time of MCI diagnosis, and had worse cognitive performance, lower body mass index (BMI), lower CSF ²-amyloid, and higher t-tau and p-tau. MCI-SNAP included more women, APOE4 carriers, and family history of dementia. In both groups, poorer cognitive performance, higher age and t-tau were associated with higher risk of progression to dementia. In the MCI-SNAP group, lower BMI was additionally associated with higher risk of dementia. Among MCI-normal CSF patients, higher p-tau and systolic blood pressure, and lower β-amyloid and fewer depressive symptoms were associated with increased risk of dementia. Other characteristics did not predict progression to dementia.

Conclusions: Predictors of dementia may be different among memory clinic patients with MCI and SNAP, compared to patients with MCI and normal CSF biomarkers.

P38

MODELLING ALZHEIMER'S DISEASE USING HUMAN CORTICAL CEREBRAL ORGANOIDS

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Rationale: Alzheimer's disease (AD) is a progressive neurodegenerative disease and presents a considerable economic burden for the society, not to mention the personal tragedies suffered by the affected patient, family and friends. Due to the age-dependant prevalence of AD, the number of cases is expected to rise as life expectancy increases. The attempts to find effective treatments are hampered by lack of clinically relevant disease models.

Methods: In response, we have started to develop a human AD model based on the cerebral organoid protocol published recently, using induced pluripotent stem cells (iPSCs). Currently, we are in the process of generating immunocompetent organoids by incorporating microglia. To this end, we have differentiated microglia from iPSCs using a protocol developed in our group. We have then incorporated the microglia into cerebral organoids and will next consolidate the microglial identity in the organoid environment by immunohistochemical profiling and response to lipopolysaccharide. Our subsequent aims are to study the microglia-synapse interactions and microglial phagocytosis of amyloid-beta aggregates and determine individual genotypic differences in immunocompetent organoids generated from iPSCs of AD and healthy genetic background. To simulate AD-pathology, we will generate the immunocompetent organoids from iPSCs derived from AD patients carrying the Swedish mutation in amyloid precursor protein, as well as isogenic and healthy control iPSC lines.

Conclusion: Consequently, our research aims to serve as the proof-of-concept for utilising immunocompetent organoid model as a clinically relevant human platform to study immune responses occurring in AD.

P39

CERAD-NB SUBTESTS AND PROGRESSION RATE IN ALZHEIMER'S DISEASE: 3- YEAR ALSOVA STUDY

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Rationale: The objective of this study was to determine the value of the cognitive subtests included in CERAD test battery, especially verbal recall which is t ypically deteriorated in AD, to predict progression of Alzheimer's disease (AD). Recognition of the persons with AD in risk of fast disease progression would be particularly useful to be able to appropriately plan care and support services.

Methods: This study is part of the longitudinal ALSOVA study with 236 persons with AD. All the persons with AD had very mild or mild disease at baseline. CERAD-NB was carried out at baseline and annually for 3 years AD progression was evaluated with change of CDR-sob (Clinical Dementia Rating scale). The disease progression was graded as slow, moderate or fast on the basis of CDR-sob change.

Results: At baseline, the slow (SG, N=74), moderate (MG, N=82) and fast progression (FG, N=80) groups did not statistically differ from each other in their demographic values or in CDR-SOB. Our results indicate that low baseline scores in CERAD's Wordlist Delayed recall does not correlate to the progression rate of AD but, there was a significant main effect between groups in three CERAD subtests at baseline.

Conclusions: It seems that other CERAD subtests than delayed verbal learning may be associated with more rapid AD aggravation. CERAD-nb carried out at the time of diagnosis may provide useful information for health care professionals to plan health care services for AD patient already at the very beginning of the disease process.

P40

NOVEL THERAPEUTIC STRATEGY TO PREVENT THE LOSS OF BDNF SIGNALING IN ALZHEIMER´S DISEASE

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Clinical studies directed to remove Amyloid-beta (Aβ) from Alzheimer's Disease (AD) patients did not demonstrate clear benefits, suggesting that Aβ toxic effects cannot be totally reverted. Therefore new strategies to prevent the Aβ irreversible impact are required. BDNF is a neurotrophin that promotes neuronal survival and synaptic plasticity through TrkB-Full Length (TrkB-FL) receptor activation. It is well described that BDNF signaling is impaired in AD and we found that Aβ induces TrkB-FL cleavage, originating a truncated receptor and an intracellular fragment (TrkB-ICD). Considering the hypothesis that TrkB-FL fragments could have toxic effects propagating Aβ toxicity, this work aimed to evaluate its presence in human AD-related neurofibrillary pathology samples, to study the role of TrkB-ICD fragment and to design and test a new drug to prevent TrkB-FL cleavage. In human brain samples, through proteomic analysis, we detected calpains activation, decreased TrkB-FL levels and increased TrkB-ICD levels in relation to increasing AD-related neurofibrillary pathology. In vitro experiments revealed that TrkB-ICD is a stable fragment, accumulates within the cell nucleus overtime and has tyrosine kinase activity. After a structural prediction, using PEP-FOLD software, a new drug was designed to act as a calpains substrate (TAT-TrkB). Remarkably, TAT-TrkB prevented TrkB-FL cleavage in neuronal cultures incubated with Aβ, prevented hippocampal LTP impairment caused by oligomeric Aβ and rescued BDNF function upon glutamate release. These data strongly suggest that TrkB-ICD have a role on AD pathophysiology and that the selective prevention of TrkB-FL cleavage could be a good strategy to prevent the loss of BDNF signaling.

P41

AMIDATED-KYOTORPHIN AS A NEUROPROTECTIVE DRUG FOR ALZHEIMER'S DISEASE

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Kyotorphin (KTP) is an endogenous dipeptide, L-tyrosyl-L-arginine, initially described as an analgesic. Interestingly, in cerebrospinal fluid of AD patients the levels of KTP are decreased, and chronic administration of an amidated form (KTP-NH2) that crosses the blood brain barrier, to a rat AD model prevents learning and memory impairments by an unknown mechanism. In this work, we studied the effects of both KTP and KTP-NH2 upon hippocampal synaptic plasticity and loss of endogenous BDNF neuroprotection. Field-excitatory post-synaptic potentials were recorded from the CA1 area of mice hippocampal slices. The effects of both forms of KTP (50nM) upon long-term potentiation (LTP) and post-tetanic stimulation (PTP) were evaluated. In addition, we analysed the effect of KTP-NH2 (co-)incubation on slices exposed to Aβ (200nM) for 3h. Since the loss of endogenous BDNF neuroprotection is associated by TrkB-FL receptors cleavage leading to the formation of TrkB-ICD fragment, we evaluated TrkB-ICD/TrkB-FL ratio by western-blot, using primary neuronal cultures incubated with KTP-NH2 (50nM) and/or Aβ (25μM) for 24h. Our results show that the incubation with KTP-NH2 restores LTP impairment in slices exposed to Aβ ($p<0.05$, N=4). KTP-NH 2 also prevents TrkB-FL cleavage induced by Aβ ($p<0.05$, N=6). Interestingly, the superfusion of both KTP and KTP-NH2 does not affect LTP magnitude (N=6-8), however KTP- NH2 increases PTP ($p<0.05$, N=6). In summary, these findings are in accordance with the results obtained previously using AD rat model. The memory deficits observed in these animals could be explained by LTP impairment caused by TrkB-FL decreased levels, both effects being rescued by KTP-NH2.

P42

MULTIMODAL PREVENTIVE TRIAL FOR ALZHEIMER'S DISEASE (MIND-ADMINI): PILOT STUDY DESIGN AND PROGRESS

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Rationale: Patients with prodromal Alzheimer's disease (AD) are an increasing group with no available interventions. The 6-month MIND-ADMINI multinational pilot trial is testing the feasibility of a multidomain lifestyle intervention in prodromal AD.

Methods: Participants with prodromal AD aged between 60 and 85 years are randomized into three groups: (1) usual care (control), (2) multidomain lifestyle intervention combining nutritional guidance, cognitive training, exercise and careful monitoring of vascular risk factors, or (3) multidomain lifestyle intervention plus medical food (specific multinutrient combination, Fortasyn Connect). The multidomain lifestyle intervention is based on the Finnish geriatric Intervention study to prevent cognitive impairment and disability (FINGER) model.

Results: Over 50 participants have been recruited in Sweden (Stockholm) and Finland (Kuopio), and additional sites in France (Toulouse) and Germany (Frankfurt) are about to start recruitment. Feed-back from participants has been very positive. An optional 6-month extension of the trial will also be conducted at the Stockholm site. Here we will present baseline characteristics of individuals recruited in the trial so far, including physical activity assessed using accelerometer data.

Conclusions: The MIND-ADMINI pilot trial will provide an intervention model feasible for patients with prodromal AD in memory clinic settings. This intervention model will then be tested in a larger trial to investigate effects on cognitive decline and dementia develop.

P43

INVESTIGATING THE BIOLOGICAL MECHANISMS UNDERLYING ALTERATIONS IN COGNITION FROM THE MULTIMODAL INTERVENTION STUDY FINGER

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Rationale: The multimodal intervention strategy tested in the FINGER trial showed very promising results in elderly at risk for dementia. After the 2-year follow-up there was a significant improvement in the intervention group. In the current study we wanted to elucidate the relationship between cardiovascular risk factors such as cholesterol and its oxygenated derivative 27-hydroxycholesterol for glucose uptake in the brain.

Methods: We utilized mass spectrometry to determine the levels of serum cholesterol, 27-hydroxycholesterol (27-OH) and 24-hydroxycholesterol (24-OH) in a subset of the FINGER participants that had been deeper characterized by positron emission tomography and magnetic resonance (PET) imaging. We used STATA to analyze the data-set.

Results: Compared to total cholesterol levels, 27-OH had a stronger correlation with high systolic blood pressure, low glucose uptake in the brain and a high level of white matter hyper-intensities.

Conclusions: The epidemiological risk factors for AD are not always easily translated into molecular mechanisms in the cell. Cardiovascular risk factors contribute greatly to AD risk, still our understanding of the underlying mechanisms is not well characterized. The current study show that 27-OH may be an important risk factor for decreased cognitive function in elderly. Gaining a deeper understanding of the mechanisms involved in the FINGER study may not only improve the design of interventions but also contribute to the exploration of new drug targets for AD.

P44

CORTISOL, COGNITION AND ALZHEIMER'S DISEASE BIOMARKERS AMONG MEMORY CLINIC PATIENTS

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Rationale: The goal is to investigate the relationship between stress and cognitive function among memory clinic patients, and the role of the Alzheimer's disease (AD) biomarkers beta-amyloid (A^2) and tau in this association.

Method: The pr esent study was cross-sectional. 138 participants were recruited from Karolinska University Hospital memory clinic in Huddinge, Sweden. Cognition was measured using two cognitive domains (memory and overall cognition), operationalized as average z-scores. Stress was assessed through the Perceived Stress Scale and four measures of salivary cortisol: awakening levels, bedtime levels, the cortisol awakening response, and total daily output. The AD-related biomarkers Aβ, total tau (T-Tau), and phosphorylated tau (P-Tau), all measured in the cerebrospinal fluid, were included as ratios: T-Tau/Aβ & P-Tau/Aβ. Linear and logistic regressions were conducted for the analyses.

Results: The cortisol awakening response was significantly associated with memory (OR = 1.75, 95% CI: [1 .12 - 2 .74]), while bedtime cortisol was inv ersely associated with overall cognition (OR = .51, 95% CI: [.28 - .95]). Controlling for the AD biomarkers did not alter these associations. Perceived stress was not associat ed with cognition. A h igher cortisol awakening response was correlated with greater AD pathology, indicated by high T-Tau/Aβ (b = .11; 95% CI: [.00 - .22]), and high P-Tau/Aβ (b = .14; 95% CI: [.01 - .26]).

Conclusions: The results of this study support the evidence that a relationship exists between cortisol and cognition. Although cortisol levels are associated with AD pathology, the relationship between cortisol and cognition does not appear to be explained by the AD biomarker ratios.

P45

GENERATION OF MICROGLIA-LIKE CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS

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Rationale: Microglia are the resident immune cells of the central nervous system with a diversity of functions in supporting homeostasis of the brain. Improper microglial activation is ce ntral to the pathology of multiple neurodegenerative diseases such as Alzheimer's disease. Currently it is unfeasible to study human microglia, because of limited access to sufficient quantities of human brain cells.

Methods: We present a physiologically relevant in vitro protocol for a high-yield production of human induced pluripotent stem cell derived microglia (hiPSCdMG). The method mimics embryonic development of microglia, starting in yolk sac, developing through primitive hematopoietic progenitors and resulting in functional microglia.

Results: The human iPSCdMGs resemble fetal human microglia and recapitulate the functional characteristics of in vivo microglia. We show that iPSCdMGs generate through primitive hematopoiesis and express a panel of micr oglial markers such as CD45, CD11b, Iba-1 and Tmem119. Furthermore, they spontaneously phagocytose synthetic beads an d scavenge their surroundings. Phagocytic and migratory activity can be modulated with different cytokines and chemokines. Moreover, iPSCdMGs respond to inflammatory stimulus by altering their metabolism and by producing proinflammatory cytokines.

Conclusion: We co nclude that this small molecule-based differentiation method is mimicking sequential stages of embryonic development and can provide a practical system to study functionality of human microglial cells in multiple genetic backgrounds.

P46

THE DEMENTIA RISK TOOL: AN EVIDENCE-BASED MOBILE APPLICATION TO PREDICT THE RISK FOR DEMENTIA

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Rationale: Effective detection of demographic and lifestyle risk factors can facilitate dementia risk reduction and prevention initiatives. While risk scores have been developed to detect the risk for dementia, there is a need for user-friendly tools that are widely accessible.

Methods: The Dementia Risk Tool mobile Application (App) was developed based on the original CAIDE Dementia Risk Score, which is validated to predict late-life dementia risk (20 years later), based on midlife (demographic, vascular and lifestyle) risk factors. The App also includes recently developed risk scores that can predict dementia based on late-life risk factors.

Results: The App was recently launched, and is available for both Android and iPhone, with a user-friendly design. Users are asked to enter information on demographic, vascular and lifestyle factors, such as age, education, height & weight, physical activity, blood pressure, and depressive symptoms. The App then calculates the user's risk score, and provides guidance on how to improve the risk factors. If needed, the user is advised to consult a health care practitioner. The App is free of charge for all users.

Conclusions: The Dementia Risk Tool is the first evidence-based App that includes validated risk scores for different age groups, and can be used by individuals or health professionals. The App can be used as a motivational and educational tool, and aid in implementing healthy lifestyle changes for dementia risk reduction. The App can also be used in research studies, for assessment of dementia risk, and for recruitment into trials.

P47

L-TYPE AMINO ACID TRANSPORTER FUNCTION IS NOT ALTERED AT THE BLOOD-BRAIN BARRIER A ND IN PRIMARY ASTROCYTES OF ALZHEIMER`S DISEASE TRANSGENIC MICE

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L-Type amino acid transporter (LAT1) is capable of delivering neuroprotective agents, such as levodopa, into the brain. However, the LAT1 expression and function at the blood-brain barrier (BBB) or brain cells in neurodegenerative diseases, like Alzheimer┤s disease (AD) is not known. The objective of this study was to evaluate the effect of AD-phenotype and lipopolysaccharide (LPS)-induced neuroinflammation on the function of LAT1 at the mouse BBB, as well as LAT1 expression and function in mouse primary astrocytes. The function of LAT1 at the BBB was evaluated in wild type (wt) mice, with and without LPS-induced neuroinflammation and APdE9 transgenic mice by in situ brain perfusion using [14C]-L-leucine as a probe substrate. LAT1 expression (mRNA and protein) and function ([14C]-L-leucine uptake) was determined in astrocytes isolated from the brain of wt and AD-mice with and without LPS-induced inflammation. The results showed that there were no statistically significant differences in [14C]-L-leucine BBB permeation among wt, LPS-treated and AD-mice. Moreover, the differences in kinetic parameters of [14C]-L-leucine in LPS-treated and AD-astrocytes compared to the wt-astrocytes were not statistically significant. Therefore, these results show that neither AD-phenotype nor LPS induced neuroinflammation alter LAT1 function at the BBB. Furthermore, the expression and function of LAT1 in astrocytes of wt or AD-transgenic mice treated with LPS was retained at the normal level. Thus, it can be concluded that LAT1 is a feasible carrier for the targeted delivery of neuroprotective drugs into the brain exposed to the neuroinflammation or neurodegeneration.

P48

BRAIN LOCALIZATION OF LEUCINE-RICH ALPHA2-GLYCOPROTEIN AND ROLE

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Objectives: We have previously reported that levels of leucine-rich alpha2-glycoprotein (LRG) expression are specifically increased in cerebrospinal fluid of idiopathic normal-pressure hydrocephalus, but function and localization in the brain remain unknown. This study aimed to examine the localization of LRG expression in the brain.

Methods: Histological sections of autopsied brain specimens from 10 subjects, comprising 5 middle-aged cases (mean age, 43.6 years; range, 34-50 years) and 5 elderly cases (mean age, 76.0 years; range, 67-88 years) were prepared and stained with antibodies against human LRG, glial fibrillary acidic protein, and aquaporin-4 (AQP4) reviewed for expression sites of LRG.

Results: LRG immunoreactivity is distributed throughout the entire brain, with particularly high expression in astrocytes of the deep cerebral cortex and hippocampus and Purkinje cells of the cerebellum. In addition, LRG immunoreactivity was observed in resident astrocytes, as well as in the capillary vessels to which astrocytic processes grow and adhere. When age-related comparisons were made between senile and adult specimens, mean (±SD) numbers of positive cells in adult and senile cases were 8.68±3.05/field and 47.68±4.18/field, respectively (t-test, $p<.01$). Numbers of LRG-immunostaining astrocytes increased with age. Relationship of LRG to AQP-4, very intense AQP-4 immunoreactivity was detected in the perivascular astrocytes and decreased with aging.

Conclusions: The expression of LRG in the brain was found to be localized in the deep cerebral cortex. This included expression in astrocytes and processes, with significant expression in the processes around blood vessels. LRG expression in the brain increased with age.

P49

SIMPLIFYING MEDICATION REGIMENS IN RESIDENTIAL AGED CARE: THE SIMPLIFICATION OF MEDICATIONS PRESCRIBED TO LONG TERM CARE RESIDENTS (SIMPLER) STUDY

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Rationale. The high prevalence of polypharmacy, together with a multiplicity of medication administration times, formulations and special dosing instructions, means that complex medication regimens are common in residential aged care facilities (RACFs). More than half of all residents of Australian RACFs have diagnosed dementia. Strategies to reduce unnecessary medication complexity are likely to be valued because complex regimens can be burdensome for residents and nursing staff.

Methods. SIMPLER is a non-blinded, matched-pair, 36-month cluster randomised controlled trial of a single multidisciplinary intervention to simplify medication regimens in South Australians RACFs. A validated, five-item tool was used to assess medications taken by residents in the intervention arm and identify opportunities to reduce the number of medication administration times. The primary outcome is the total number of medication administration times per day at four months post-study entry. Secondary outcomes include time spent administering medications, medication incidents, resident satisfaction and quality of life, hospitalisations, falls and mortality.

Results. Trained study nurses recruited 242 permanent residents from eight RACFs between April and October 2017. The median age of participating residents was 87 years and 179 (74%) were female. Of the 96 residents who received the intervention, opportunities for medication regimen simplification were identified for 62 (65%) residents. Collection and analysis of four month follow-up data is ongoing.

Conclusions. SIMPLER will enable an improved understanding of the burden of medication use in RACFs and quantify the impact of medication regimen simplification on a range of outcomes that are important for residents and aged care providers.

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The 8th Kuopio Alzheimer Symposium is organised by the University of Eastern Finland, Institute of Clinical Medicine–Neurology and the Doctoral Program in Molecular Medicine. The scientific program features new and inspiring research findings on neurodegeneration, diagnosis and prediction of Alzheimer's disease and other neurodegenerative diseases. It also brings an update on biomarker studies, new advances in imaging, disease models and prevention, population-based prevention studies. The Finnish Session "Memory Day" concentrates on the impact of intoxicants, exercise and nutrition on cognition and the interaction of gut and brain.

This book contains the program and abstracts of the 8th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 6-8, 2018.

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