Metabolomics in Alzheimer's Disease

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Journée Métabolomique Bilille
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ALZHEIMER'S DISEASE (AD)

Epidemiology

- 30-35 million people worldwide, main cause of dementia
- Early versus late onset AD
- Monogenic versus multifactorial disease

Diagnostic

- AD *vs* Mild Cognitive Impairment (MCI) *vs* Cognitively Normal (CN)
- Cognitive assessment
- Aβ, Tau and p-Tau levels
- MRI, PET (atrophy of brain regions, white matter hyperintensities)

METABOLOMICS IN DISEASES

- **Why should we focus on metabolomics ?**
  - Analysis of metabolomic signatures and their components can potentially provide information with regard to disease pathophysiology
  - Disease states perturb biochemical network -> new metabolomic signature
  - New diagnostics markers
- **Analyses**
  - Association
  - Classification/Prediction

Application of metabolomics in AD

- **Many studies**
- **But …**
  - Several different platforms
  - Many different panels
  - Many different sample types (blood, brain, CSF, saliva)
  - Most studies with few samples (~50-200 samples)
- **Interpretation not reliable**

Association studies

ASSOCIATION STUDIES

Toledo et al., 2017

- Sample type: Serum
- Platform: HPLC-MS/FIA-MS
- N metab. = 186
- Samples:
  175 AD
  199 controls

Van der Lee et al., 2018

- Sample type: Plasma
- Platform: NMR
- N metab. = 15*
- Samples:
  1,405 AD
  25,972 controls

Tynkkynen et al., 2018

- Sample type: Serum
- Platform: NMR
- N metab. = 299
- Samples:
  Discovery:
  178 AD
  14,654 controls
  Replication:
  466 AD
  6,330 controls

Mahmoudian-Dehkordi et al., 2019

- Sample type: Serum
- Platform: LC-MS
- N metab. = 15 (BA)
- Samples:
  305 AD
  370 controls

Varma et al., 2018

- Sample type: Serum
- Platform: HPLC-MS/FIA-MS
- N metab. = 188
- Samples:
  92 converters
  115 non-converters

BA: Bile acids

* Found as associated with general cognitive decline in the same study

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Association studies: What do we know?

Cholesterols sub-fractions	Amino acids	Phospholipids	Bile acids	Other classes
S-HDL-FC M-HDL-PL L-HDL-CE	Glutamine Isoleucine Leucine Valine	SM C16:0 SM C16:1 SM (OH) C14:1 SM C18:1 PC aa C38:4 PC ae C34:2	CA ; DCA GDCA ; TDCA GLCA ; TLCA	DHA

Cholesterols sub-fractions: HDL: High density lipoprotein; S-HDL-FC: *Free cholesterol in small HDL*; M-HDL-PL: Phospholipids in medium HDL; L-HDL-CE: *concentration of choloesterol esters relative to total lipids in large HDL*
Phospholipids: SM: Sphingomyelin; SM (OH): Hydroxysphingomyelin; PC aa: Phosphatidylcholine with diacyl residue; PC ae: Phosphatidylcholine with acyl-alkyl residue
Bile acids: CA: *Cholic acid*; DCA: *Deoxycholic acid*; GDCA: *Glycodeoxycholic acid*; TDCA: *Taurodeoxycholic acid*; GLCA: *Glycolithocholic acid*; TLCA: *Taurolithocholic acid*
Other classes: DHA: *Docosahexaenoic acid*

Association studies: What's next?

- **Roles of identified metabolites in AD?**
  - Etiologic roles in development in AD
  - Early biomarkers of the pathology
- **Identified metabolites as readouts for preventive and therapeutic interventions?**
- **Prevention of AD by selective interventions targeting metabolites**
- **Needs for a further investigation of the possible role of gut-liver-brain axis in AD pathogenesis**

Classification/Prediction

CLASSIFICATION/PREDICTION: STUDIES

Ibanez et al., 2012

- Sample type: CSF
- Platform: CE-MS
- N metab. = 160
- Samples:
  - Training:
    - 23 AD
    - 9 MCI-AD
    - 41 non-AD
  - Testing:
    - 2 AD
    - 4 MCI-AD
    - 6 non-AD

Koal et al., 2015

- Sample type: CSF
- Platform: HPLC-MS/FIA-MS
- N metab. = 185
- Samples:
  - 50 AD-like
  - 50 CN

Fiandaca et al., 2015

- Sample type: Plasma
- Platform: UPLC-MS
- N metab. = 184
- Samples:
  - Training:
    - 23 pheno-converters
    - 53 CN
  - Testing:
    - 10 pheno-converters
    - 20 CN

Varma et al., 2018

- Sample type: Brain
- Platform: HPLC-MS/FIA-MS
- N metab. = 187
- Samples:
  - 15 AD
  - 15 ASYMAD
  - 14 CN

Yilmaz et al., 2019

- Sample type: Saliva
- Platform: NMR
- N metab. = 57
- Samples:
  - 9 AD
  - 8 MCI
  - 12 CN

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CLASSIFICATION/PREDICTION: RESULTS

- **Panels from 1 to 26 metabolites use to discriminate AD, MCI and CN samples**
- **Performance of the models**
  - Accuracy from 69% to 95%
  - Sensitivity from 90% to 100%
  - Specificity from 59% to 95%
  - AUC from 0.83 to to 0.90
- **But, some weaknesses:**
  - Small sample sizes
  - Training/Testing validation not always done
  - Validation in larger and independent dataset never done
  - Overestimation of models performance

Conclusions

CONCLUSIONS

- **Identification of metabolites associated with AD**
- **Role of the gut-liver-brain axis in AD**
- **Classification/prediction models still at their beginning**
  - Multi-omics models
- **Requires significant effort to define biomarkers that are predictive and disease-specific**
  - Concomitant disease could affect metabolic profile

Institut Pasteur de Lille

Vivre mieux plus longtemps

Thank you!