Neuroinflammation in preclinical AD: in vivo evidence

Barbara Bendlin, PhD
Assistant Professor
UW-Madison Dept. of Medicine, Geriatrics
bbb@medicine.wisc.edu
Overview

- Background
- Preclinical effects of neuroinflammation
- Future directions

No conflicts of interest.
NFT
Beta-amyloid
Neuronal/synaptic loss
Inflammatory cascade

Epidemiological studies

- Prevalence of AD was only 0.4% in arthritis patients
- Rotterdam study, Cache County, BLSA
- 50% decrease in risk for developing AD in NSAID users.

http://www.sfn.org/~media/SfN/Documents/TheHistoryofNeuroscience/Volume%203/c11.ashx
Animal studies

- LPS induced inflammation in rats will result in a pattern similar to pattern in AD.
Human post mortem

- Microglia differentiate symptomatic AD

Treatment trials in AD

- NSAID trials in dementia
- NSAID trials in MCI
- ADAPT trial discontinued
- Follow-up: reduction in AD incidence among symptomatic enrollees given naproxen

Anti-inflammatory effects on human brain

- Preserved gray matter volume in RA patients


- and NSAID users.

Given that inflammation may play a role in the early stage development of AD...

- What is the effect of preclinical inflammation on the brain?
Preclinical

- Participants with risk
- Parental FH
- APOE4
In vivo markers

- **MRI**
  - Volumetric
  - Microstructure
  - Blood flow
  - Functional

- **PET**
  - FDG
  - PiB
  - PBR28

- **CSF**
  - Aβ42, sAPPβ
  - T-Tau, P-Tau, NFL
  - IL6, IL8, TNFalpha
  - MCP-1, YKL-40

- **Plasma**
  - IL6, IL8, IL10, IL1β, HS-CRP, TNFalpha
In vivo markers

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CSF markers

- YKL-40 secreted by activated microglia
- Increased CSF YKL-40 described in early-stage AD (Craig-Schapiro et al. 2010).
- YKL-40 obtained using ELISA (Zetterberg)
- Aβ42 obtained via X-MAP
- Complementary markers included MCP-1, sAPPβ, T-Tau, and P-Tau181

http://en.wikipedia.org/wiki/CHI3L1

• Inflammation may cause neuronal damage
• Amyloid deposition is toxic to neurons
• Aβ42 aggregates into oligomers along microtubules of neuronal processes
• AD involves hyperphosphorylation of tau protein, resulting in axonal abnormalities
Study Summary

- Participants with risk (Parental FH, APOE4)
- Underwent brain imaging and lumbar puncture
- CSF sample were assayed for markers related to Aβ and microglia
- Overarching hypothesis: greater microglial activation, altered microstructure
Models

- Regression
- Main effects: YKL-40
- YKL-40 x risk (APOE4 & FH)
- YKL-40 x amyloid (Aβ42)
- Covariates: Age, sex
- Indices of microstructure: FA & MD
Demographics

- N = 97 (cog. healthy, MMSE mean = 29.36)
- age range = 49 – 72 years
- mean = 62 years
- 36% APOE4+
- 72% FH+
- 64 women, 33 men
Results: DTI and Age

- Effect of age on 12/14 measures
  - (all but cingulum-HC FA & SLF MD)
Results: YKL-40, risk and Aβ

- YKL-40: range: 49.99-320.30 ng/mL, mean = 144.57 ng/mL
- YKL-40 did not differ between FH or APOE4 risk groups
- YKL-40 was positively correlated with sAPPβ (r = .54, p < .001) and Aβ42 (r = .37, p<.001)*
- No main effects of YKL-40 on the DTI measures

* Controlling for age
YKL-40 interacts with APOE4

- Splenium FA
- $p = .022$
YKL-40 interacts with APOE4

- Cingulum FA
- \( p = .011 \)
YKL-40 interacts with APOE4

- Cingulum-HC FA
- \( p = .005 \)
YKL-40 interacts with APOE4

- Genu MD
- $p = .046$
YKL-40 interacts with APOE4

- Splenium MD
- \( p = .013 \)
YKL-40 and Aβ42...

- Weak trend
- Low Aβ42 + higher YKL-40 = higher diffusivity
- Splenium MD (p = .089)
Summary

- YKL-40 levels did not differ by FH or APOE4 risk groups

- YKL-40 was related to markers of amyloid (sAPPβ, Aβ42)

- APOE4 + microglia was associated with altered microstructure

- Vulnerability due to APOE4

- Axonal loss in presence of inflammation?

Axons have tau-bound microtubules.
Conclusion & Future Directions

- Evidence for preclinical relationship
- Timing is important: dampen inflammation or exploit immune response?
- Future: additional participants, markers, longitudinal data
- Regional pattern of inflammation: [11C]PBR28

Puglielli et al. in prep.
Wisconsin ADRC
CSF Working Group

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