Neuropathology of neurodegenerative diseases in Toronto: Accomplishments and challenges

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Human Resources

- 8.5 Neuropathologists in Toronto
  - 3 UHN
  - 1.5 Sunnybrook
  - 2 Hospital for Sick Children
  - 1 Mount Sinai
  - 1 St. Michael’s

- 2 Primary interest in dementia
  - L-N H, DGM
Canadian Brain Tissue Bank 1

- Established 1982
  - Initially managed by the Canadian Neurological Coalition

  - Support
    - Medical Research Council
    - Ontario Mental Health Foundation
    - Canadian Neurological Coalition
  - Budget 150K-200K/yr
  - 120 brains/yr
  - Staff:
    - 2 Office staff, 1 Tissue Coordinator, 1 Medical Director
Canadian Brain Tissue Bank 2

- 1992-2000
  - Reduced budget to 25% of prior
  - Reduced donors
  - No detailed frozen tissue dissections

- 2000-2010 (gradual)
  - No donations
  - No staff
  - Tissue stored in freezers at UHN
  - Retrievals continue as part of collaborative studies
Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions


Frontotemporal lobar degeneration (FTLD) is the second most common type of familial dementia after Alzheimer disease. Mutations in \textit{GRN}. Our data implicate variants in \textit{TMEM106B}.


**CBTB current status**

**Assets**

- Collection of >300 frozen & histological brain samples of well clinically characterized patients
- Interested & dedicated neuropathologists
- Good facilities

**Liabilities**

- Lack of stable funding
CBTB: Potential

- Pathological confirmation of presumed diagnosis for numerous ongoing clinical studies in Toronto
  - Source of donations
- Fresh frozen tissue for basic researchers
- Further delineation of neurodegenerative diseases through clinico-pathological correlation studies
- Stable funding only missing factor
STRUCTURAL CORRELATE OF FOCAL SIGNS IN ALZHEIMER’S DISEASE

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Argyrophilic thorny astrocyte clusters in association with Alzheimer’s disease pathology in possible primary progressive aphasia

David G. Munoz · John Woulfe · Andrew Kertesz
Unresolved questions

- Clinical profile of patients with PPA and AD pathology
- In cases with AD pathology, pathological differences between cases
  - with PPA symptoms
  - without PPA symptoms
- Is the focal presentation related to
  - Selective regional distribution of plaques and tangles
  - Additional presence of a different lesion
ALL CASES

Pathological Diagnosis:

- Alzheimer’s Disease
- Abundant NP & NFT
- Braak stage V-VI
- Typical distribution
ATAC: Argyrophilic Thorny Astrocyte Clusters
7 out of 8 cases
Eccentric nucleus
Stout perikarya
Coarse dense clumps
Thorny outline
ATAC characterization

Location

- Cerebral cortex
- Subcortical WM (near GWJ)
- Absent subcortical GM

Unrelated to

- Myelin pallor (leukoaraiosis)
- Gliosis
- Infarcts
- NFT density
- Plaque density
CONCLUSIONS: ATAC

- ATAC are a common, but not universal co-substrate of PPA in AD
- ATAC differ from ATA in normal aging
  - Location, most Gallyas +
- Intensification of aging changes vs independent phenomenon
  - Neuronal NFT:
    - Aging ≈ AD
    - Aging ≠ PSP, CBD
- Hypothesis: ATAC represent a marker of a process responsible for or contributing to the prominent focal clinical manifestations in AD
Finds aphasia in AD
- poorly related to NFT, plaque distribution.
- ATAC in subset of cases

Alzheimer and Frontotemporal Pathology in Subsets of Primary Progressive Aphasia

Marsel Mesulam, MD, Alissa Wicklund, PhD, Nancy Johnson, PhD, Emily Rogalski, PhD, Gabriel C. Léger, MD, Alfred Rademaker, PhD, Sandra Weintraub, PhD, and Eileen H. Bigio, MD.
Ongoing collaboration

- Structural substrate of focal signs in AD
  - Black, Bilbao (Sunnybrook)
  - Munoz (St. Michael’s)
FUSOPATHIES
Relationship between aFTLD-U, NIFID, & BIBD
Black, Bilbao (Sunnybrook)
Munoz (St. Michael’s)

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ORIGINAL PAPER

FUS pathology in basophilic inclusion body disease

David G. Munoz · Manuela Neumann · Hirofumi Kusaka · Osamu Yokota · Kenji Ishihara · Seishi Terada · Shigetoshi Kuroda · Ian R. MacKenzie
What we need

- Stable funding to support a Brain Bank
  - Strengthen clinical studies by confirming diagnosis
    - Improved QA, basic-clinical link
  - Histological studies
  - Biochemical studies
  - Imaging correlation
  - Strengthen genetic studies

- We have the capability. With funding support as an outcome of this alliance we will be in a position to re-start this program