Poster #192

A LOW MOLECULAR WEIGHT FERROXIDASE IS INCREASED IN THE CSF OF SCJD CASES: CSF FERROXIDASE AND TRANSFERRIN AS DIAGNOSTIC BIOMARKERS FOR SCJD

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(Presented By: Neena Singh)

Aims: Most biomarkers used for the pre-mortem diagnosis of sporadic Creutzfeldt-Jakob disease (CJD) are surrogate in nature, and provide suboptimal sensitivity and specificity.
Results: We report that CJD-associated brain iron dyshomeostasis is reflected in the cerebrospinal-fluid (CSF), providing disease-specific diagnostic biomarkers. Analysis of 290 pre-mortem CSF samples from confirmed cases of CJD, Alzheimer's disease, and other dementias, and 52 non-dementia controls revealed a significant difference in ferroxidase (Frx) activity and transferrin (Tf) levels in sCJD relative to other dementia and non-dementia controls. A combination of CSF Frx and Tf discriminated sCJD from other dementias with a sensitivity of 86.8%, specificity of 92.5%, accuracy of 88.9%, and area under the receiver-operatingcharacteristic (ROC) curve of 0.94. This combination provided a similar diagnostic accuracy in discriminating CJD from rapidly-progressing cases that died within 6 months of sample collection. Surprisingly, ceruloplasmin and amyloid-precursor-protein, major brain ferroxidases, displayed minimal activity in the CSF. Most of the Frx activity was concentrated in <3 kDa fraction in normal and disease CSF, and resisted heat and proteinase-K treatment.
Discussion: 1) A combination of CSF Frx and Tf provide disease-specific pre-mortem diagnostic biomarkers for sCJD. 2) A novel, non-protein Frx predominates in human CSF that is distinct from the currently known CSF ferroxidases.
Conclusion: The underlying cause of iron imbalance is distinct in sCJD relative to other dementias associated with brain iron imbalance. Thus, change in CSF levels of iron-management proteins can provide disease-specific biomarkers and insight into the cause of iron-imbalance in neurodegenerative conditions.

Poster #193

IRON: KEY TO INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY TO PESTICIDE NEUROTOXICITY?

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Introduction: Chemical pesticides, especially those applied in agriculture, are suspected to be risk factors for neurodegenerative diseases such as Parkinson's disease. Epidemiological studies, however, report inconsistencies in rates of relative risk for those exposed to pesticides such as Rotenone, Maneb. and Paraquat (PQ). PQ is an herbicide used world-wide, except for the European Union. In addition to its herbicidal effects, PQ is highly toxic to mammalian lung, and in animals PQ has been shown to be neurotoxic. A major target of PQ neurotoxicity is the substantia nigra pars compacta (SNc), and this region's population of dopaminergic neurons. Degeneration of these cells with subsequent loss of dopamine in the caudate-putamen is the primary pathophysiological feature of idiopathic Parkinson's disease.
Methods and Materials: We recently showed that differential susceptibility to PQ neurotoxicity in four inbred mouse strains from the family of BXD recombinant inbred strains is associated with the increase in iron concentration in the ventral midbrain – the area containing both the SNc and ventral tegmentum. In comparing the effect of PQ on gene expression in the ventral midbrain, one PQ-susceptible strain showed changes in more than 300 transcripts whereas one resistant strain showed changes in fewer than one dozen transcripts.
Results: In the sensitive strain, the preponderance of genes with altered expression is iron binding protein genes; whereas in the resistant strain, the few altered genes are related to intermediate metabolisms. While we have shown the likely involvement of iron in PQ-related dopamine neurotoxicity, the question remains whether the relationship between iron and PQ is unique to PQ. We also studied genetic differences among 10 BXD recombinant inbred mouse strains to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a proneurotoxicant (the active agent is the metabolite, MPP+ produced in astrocytes) used to model the pathophysiology of Parkinson's disease. Again, we detected large genetic differences in neurotoxicity produced by this agent. In the strain most susceptible to MPTP toxicity we observed a significant increase in iron concentration in the ventral midbrain.
Conclusion: Our research is not the first to show a relationship between PQ and iron in neurotoxicity. It is the first however, to show that individual differences in susceptibility to PQ and probably other neurotoxicants are related to genetic differences in toxicant-based influx of iron into the ventral midbrain, especially in the SNc.